FORMULATION AND *IN VITRO* EVALUATION OF BILAYER FLOATING TABLETS OF METFORMIN HCL AND SITAGLIPTIN PHOSPHATE

Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI – 32

In partial fulfillment for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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Under the guidance of

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MAY – 2012

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CERTIFICATES

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND *IN VITRO* EVALUATION OF BILAYER FLOATING TABLETS OF METFORMIN HCL AND SITAGLIPTIN PHOSPHATE",** submitted by the student bearing **Reg. No. 26103004** to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS** was evaluated by us during the examination held on…….

Internal Examiner **External Examiner**

CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND *IN VITRO* EVALUATION OF BILAYER FLOATING TABLETS OF METFORMIN HCL AND SITAGLIPTIN PHOSPHATE",** submitted to The Tamilnadu Dr.M.G.R. Medical University, Chennai, was carried out by **Mr. G. HEMANTH KUMAR, [Reg.NO: 26103004],** for the partial fulfillment of Degree of **MASTER OF PHARMACY** in Pharmaceutics under direct supervision of **Mr. K. JAGANATHAN, M. Pharm.,** Department of Pharmaceutics**, J.K.K. NATARAJA COLLEGE OF PHARMACY**, Komarapalayam, during the academic year 2011-2012.

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The work presented in this dissertation entitled, **"FORMULATION AND *IN VITRO* EVALUATION OF BILAYER FLOATING TABLETS OF METFORMIN HCL AND SITAGLIPTIN PHOSPHATE",** was carried out by me, under the direct supervision of **Mr. K. JAGANATHAN, M.Pharm.,** Department of Pharmaceutics, J.K.K. Nataraja College of Pharmacy, Komarapalayam.

I further declare that, this work is original and has not been submitted in part or full for the award of any other degree or diploma in any other university.

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ACKNOWLEDGEMENT

First, I would like to thank my **PARENTS** who raised me with a love of science and supported me in all my pursuits without whom i would not be where i am now.

I express whole hearted gratitude to my guide **Mr. K. JAGANATHAN**, **M.Pharm.,** Department of Pharmaceutics, J.K.K Nattraja College Of Pharmacy, Komarapalayam, for suggesting solutions to my problems and providing indispensable guidance, tremendous encouragement at each and every step of my work. Without his advice and knowledge this work would not have been a reality.

My immense privilege and profound gratitude to **Dr. P. PERUMAL, M.Pharm., Ph.D., A.I.C.,** Principal, J.K.K. Nattraja College Of Pharmacy, Komarapalayam for furnishing all the necessary facilities with whole hearted support and guidance which enabled me to complete this project work in a successful manner.

I extend my heartfelt thanks to founder, Late. **Thiru J.K.K. NATARAJAH CHETTIAR,** for providing us Master of Pharmacy Degree. I pray to god to let his soul rest in peace.

My sincere thanks and respectful regards to our beloved correspondent, **Tmt. N. SENDAMARRAI,** Managing Director **Mr. OMMSHARRAVANA, B.Com., L.L.B.,** and Executive Director **Mr. OMMSINGARRAVEL, B.E., M.S.,** for helping me with all the necessary facilities for completing my project during my tenure in the college.

I express my heartfelt thanks to **Dr. R. SAMBATH KUMAR, M.Pharm., Ph.D.,** Head, Department of pharmaceutics, **Mrs. S. BHAMA, M.Pharm.,** Department of Pharmaceutics, for their valuable suggestions during my work and presentation of my thesis .

I also convey my thanks to **Mr. VENKATESWARA MURTHY, M.Pharm., Ph.D.,** Assistant Professor and Head of the Department, **Mrs. THANGAMANI, M.Pharm.,** Department of Pharmacy Practice, for their valuable suggestions regarding selection of drug, dose etc for my project.

I express my sincere thanks to **Dr. P. SIVAKUMAR M.Pharm., Ph.D.,** Head, **Mr. M. VIJAYABASKARAN M.Pharm., Ph.D.,** Asst. Professor, **Mrs. P. VAIJAYANTHIMALA M.Pharm.,** Lecturer, Department of Pharmaceutical Chemistry, for their valuable suggestions and inspiration.

I express my sincere gratitude to **Mr. V. RAJESH, M.Pharm., Ph.D.,** Assistant Professor & Head of the Department of pharmacology for his co operation, and suggestions.

My sincere thanks to **Mr. V. SEKAR, M.Pharm., Ph.D.,** Asst. Professor & Head of Department, **Mr. D. BOOPATHY, M.Pharm., Ph.D.,** Asst. Professor, **M. SENTHILRAJA**, **M.Pharm., Ph.D.,** Asst. Professor, **Mr. S. JAYASEELAN, M.Pharm.,** Asst. Professor, Department of Pharmaceutical Analysis for their valuable suggestions regarding the Analytical work in my project.

My sincere thanks to **Dr. S. SURESH KUMAR, M. Pharm., Ph.D.,** Head of the Department of Pharmacognosy for his valuable suggestions.

My sincere thanks to **Mr. S. KANAGASABAI, M.Tech.,** Asst. Professor for his help during my project.

I wish to thank **Mr. B. MUTHU KUMARAN, Mrs. SHANTHI** Laboratory Assistants, **Mrs. V. GANDHIMATHI M.A., M.L.I.S.,** librarian, for providing necessary facilities from library at the time of work.

My special words of thanks to all other teaching and non-teaching staffs are submitted here with.

I am extremely thankful and indebted to my friends for their valuable constructive criticism, co-operation, encouragement, love and support throughout my project work.

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DEDICATED TO

MY FAMILY

AND

FRIENDS

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1. INTRODUCTION

1.1 DIABETES

Diabetes Mellitus (DM), often simply referred to as **diabetes**, is a group of metabolic diseases in which a person is mainly characterized by hyperglycemia either because of insulin deficiency or because of the resistance shown by the cells to insulin produced in the body. It may also be characterized by glycosuria, negative nitrogen balance, and sometimes ketonemia. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger).

Classification of Diabetes mellitus

Diabetes Mellitus is classified based on the cause or mode of treatments into the following types:

1. **Insulin-dependent diabetes mellitus** (**IDDM**)
2. **Non-insulin-dependent diabetes mellitus (NIDDM**)
3. **Gestational diabetes mellitus (GDM)**
4. **Secondary to other conditions**

A) Type I (or)Insulin-dependent diabetes mellitus (IDDM)

Characterized by the body's failure to produce insulin due to the destruction of β cells in the islets of langerhans, and requires the person to inject insulin. Formerly, it is known as "juvenile diabetes," because it represents a majority of the cases in children, teenagers, or young adults, but it can also affect adults. Type-1 diabetes is mostly caused by autoimmune disorder AND develops because the body immune system mistakenly destroys the beta cells in the islet tissue of the pancreas that produce insulin due to environmental factors.

For the treatment of type I insulin must be given subcutaneously or by injecting through any other novel routs of administration.

B) Type II (or)Non-insulin-dependent diabetes mellitus (NIDDM)

Characterized by insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. People can develop type 2 diabetes at any age even during childhood. This form of diabetes usually occurs because of abnormality in gluco receptor of β cells, Reduced sensitivity of peripheral tissues to insulin, Excess of hyperglycemic hormones. Insulin is not sufficient for the treatment of type II diabetes

Treatment includes (1) Agents which increase the amount of insulin secreted by the pancreas, (2) Agents which increase the sensitivity of target organs to insulin, and (3) Agents which decrease the rate at which glucose is absorbed from the gastrointestinal tract.

C) Gestational diabetes mellitus (GDM)

Diabetes develops during pregnancy and mostly disappears after delivery. During pregnancy, increased levels of certain hormones made in the placenta help take nutrients from the mother to the developing fetus. Hormones from the placenta help the baby develop. However, these hormones also block the action of the mother's insulin in her body, called insulin resistance. Insulin resistance makes it hard for the mother's body to use insulin. She may need up to three times as much insulin.

D) Secondary to other conditions

Diabetes occurring as secondary to the conditions like Pancreatic disease, Hormonal disease, Drug or chemical exposure, Insulin receptor abnormalities, certain genetic syndromes.

Signs and Symptoms :

The classical symptoms of diabetes are Polyuria (frequent urination), Polydipsia (increased thirst) and Polyphagia (increased hunger). Symptoms may

develop rapidly (weeks or months) in type 1 diabetes while in type 2 diabetes they usually develop much more slowly.

People may also present with diabetic ketoacidosis, characterized by the smell of acetone; a rapid, deep breathing known as Kussmaul breathing; nausea; vomiting and abdominal pain; and altered states of consciousness.

Diagnosis

Table no – 01 Criteria for diagnosis of diabetes:

2006 WHO Diabetes criteria[20]		
Condition	**2 hour glucose** mmol/l(mg/dl)	**Fasting glucose** mmol/l(mg/dl)
Normal	<7.8 (<140)	<6.1 (<110)
Impaired Fasting Glycaemia	<7.8 (<140)	≥ 6.1(≥110) &<7.0(<126)
Impaired Glucose Tolerance	≥7.8 (≥140)	<7.0 (<126)
Diabetes Mellitus	≥11.1 (≥200)	≥7.0 (≥126)

Epidemiology

According to recent estimates, approximately 285 million people worldwide (6.6%) in the 20–79 year age group were having diabetes in 2010 and by 2030, 438 million people (7.8%)of the adult population, is expected to have diabetes. The largest increases will take place in the regions dominated by developing economies.

The global increase in the prevalence of diabetes is due to population growth, aging, urbanization and an increase of obesity and physical inactivity. The three countries with the largest number of people with diabetes are India, China and the U.S with 50.8, 43.2, 26.8 million patients respectively.

Management

Diabetes mellitus is a chronic disease which cannot be cured except in very specific situations. Management keeps blood sugar levels as close to normal as possible, without causing hypoglycemia. This can usually be accomplished with diet, exercise, and use of appropriate medications (insulin in the case of type 1 diabetes, oral antidiabetec medications as well as possibly insulin in type 2 diabetes).

Oral Antidiabetec Drugs :

For treating type II diabetes many drugs are given through oral route of administration, they are:

1. Insulin Sensitizers

i) Biguanides: Biguanides reduce hepatic glucose output and increase uptake of glucose by the periphery, including skeletal muscle.

Examples: Metformin, Phenformin, Buformin

ii) Thiazolidinediones: Thiazolidinediones (TZDs), also known as "glitazones, are the agonists of peroxysome proliferator activated receptor PPARγ which enhances the transcription of insulin responsive genes. They tend to reverse the insulin resistance.

Examples: Rosiglitazone , Pioglitazone, Troglitazone

2. Insulin Secretagogues

i) Sulfonylureas : They are insulin secretagogues, triggering insulin release by inhibiting the K_{ATP} channel of the pancreatic beta cells. The "second-generation" drugs are now more commonly used. They are more effective than first-generation drugs and have fewer side effects. All may cause weight gain.

First generation agents: Tolbutamide, Acetohexamide, Tolazamide, Chlorpropamide .

Second generation agents: Glipizide, Glyburide, Glimepiride, Gliclazide .

ii) Meglitinides: Meglitinides help the pancreas produce insulin and are often called "short-acting secretagogues." They act on the same potassium channels as sulfonylureas, but at a different binding site.

Examples: Repaglinide (Prandin), Nateglinide (Starlix)

3. **Alpha-Glucosidase Inhibitors**:

Alpha-glucosidase inhibitors are not technically hypoglycemic agents because they do not have a direct effect on insulin secretion or sensitivity. These agents slow the digestion of starch in the small intestine, so that glucose from the starch of a meal enters the bloodstream more slowly. but can be helpful in combination with other agents in type 2 diabetes.

Examples: Miglitol (Glyset), Acarbose (Precose/Glucobay).

Novel Oral Antidiabetecs

Dipeptidyl Peptidase (DPP)-4 Inhibitors

DPP4 inhibitors such as Sitagliptin and Vildagliptin are novel agents for treatment of type 2 diabetes. They work by improving β-cell sensitivity to glucose, whereby it increases glucose-dependent insulin secretion. Gliptins can be used as monotherapy or combined with metformin or SUs. Gliptins are largely weight neutral.

Examples: Sitagliptin, Vidagliptin.

Combination therapy

However, with disease progression, in most instances, monotherapy loses efficacy over time as evidenced by a continued increase in $HbA_{1c.}$ In addition to

insulin resistance, β-cell dysfunction plays a key role in the progression of T2DM. the primary objective of combining oral antidiabetic treatments for T2DM is to address the dual problems of insulin deficiency and insulin resistance.

Metformin - The most widely used Oral Antidiabetic

Metformin, a biguanide that acts directly against insulin resistance, is regarded as an insulin sensitizing drug and is considered to be a cornerstone in the treatment of T2DM. Because of its safety and efficacy, Metformin can be initiated as first line monotherapy unless a contraindication such as renal disease, hepatic disease, gastrointestinal intolerance or risk of lactic acidosis coexists.[4] Amongst common diabetic drugs, ***Metformin is the only widely used oral drug that does not cause weight gain.***

Despite being the most widely used OAD in the world, metformin can reach a plateau of effectiveness due to progressive β-cell failure.[34,35] Thus Metformin also forms the cornerstone of dual therapy and is used extensively in combination with several classes of OADs like

i)Sulphonylurea **Ex**: Glipizide (Metaglip®), Gliclazide, Glibenclamide (Glucovance®),

ii) Glitazones **Ex**: Rosiglitazone (Avandamet®), Pioglitazone (Actoplus Met®),

iii) Meglitinides **Ex** : Repaglinide (Prandimet®).

iv) DPP-4 Inhibitors **Ex**: Sitagliptin (Janumet®),

In recent meta-analyses, Rao *et al.* have shown that combination therapy with metformin and SUs significantly increased the relative risk of cardiovascular hospitalization or mortality

Metformin Sitagliptin Combination

Metformin Sitagliptin Combination is used when initial therapy in patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise do not provide adequate glycemic control.

Combination is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus inadequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin

1.2 ORAL DOSAGE FORMS

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs through different dosage forms. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process[1].

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as[2, 3]:

1) Drugs with short half-life require frequent administration, which increase the chances of missing dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma concentration-time profile is obtained which makes it difficult to attainment of steady state condition.

3) The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the C_{SS} values fall or rise beyond the therapeutic range.

4) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs.

In order to overcome the drawbacks of conventional drug deliver systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits[4].

1.3 Controlled Drug Delivery Systems

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue[5].

Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

1) Delayed release
2) Sustained release
3) Site-specific targeting
4) Receptor targeting

More precisely, Controlled delivery can be defined as[6]: -

1) Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
2) Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.
3) Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.
4) Provide a physiologically/therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the

uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

Advantages of Controlled Drug Delivery System[7]

1. Avoid patient compliance problems.
2. Dosage frequency were reduced
   a) Minimize or eliminate local side effects
   b) Minimize or eliminate systemic side effects
   c) Obtain less potentiation or reduction in drug activity with chronic use.
   d) Minimize drug accumulation with chronic dosing.
3. Improve efficiency in treatment
   a) Cures or controls condition more promptly.
   b) Improves control of condition i.e., reduced fluctuation in drug level.
   c) Improves bioavailability of some drugs.
   d) Make use of special effects, eg. Sustained-release aspirin for morning relief of arthritis by dosing before bedtime.
4. Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with less frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced

Disadvantages

1) Decreased systemic availability in comparison to conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
2) Poor in vitro – in vivo correlation.
3) Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.
4) Retrievals of drug are difficult in case of toxicity, poisoning or hypersensitivity reactions.

5) Reduced potential for dosage adjustment of drugs normally administered in varying strengths.

Oral Controlled Drug Delivery Systems

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either local or systemic action.

Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of (i) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug (ii) the anatomic and physiologic characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed.

The main areas of potential challenge in the development of oral controlled drug delivery systems are: -

1) Development of a drug delivery system: To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.
2) Modulation of gastrointestinal transit time: To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.
3) Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.

1.4 GASTRO RETENTIVE DRUG DELIVERY SYSTEM (GRDDS)

These are the controlled drug delivery systems, with a prolonged residence time in the stomach. A major constraint in oral CRDD is that not all drug candidates are absorbed uniformly throughout the gastrointestinal tract. Some drugs are absorbed uniformly throughout the Gastro intestinal tract. Some drugs are absorbed in a particular portion of gastrointestinal tract only or are absorbed to a different extent in various segments of gastrointestinal tract. Such drugs are said to have an **"**absorption window". Thus, only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption.

Generally gastroretention was done for:

- To control (or) increase the gastric residence time (GRT).
- To delay the gastric emptying process.

Suitable Drug Candidates For Gastroretention

- Drugs that are absorbed from the proximal part of the gastrointestinal tract i.e absorption window present in upper part of the GIT . examples: Sulphonamides, Quinolones, Penicillin's, Cephalosporin's, amino glycosides, Tetracycline's etc.
- For sparingly soluble and insoluble drugs the solubility can be increased by increasing their gatric residence time there by improving bioavailability.
- Drugs that are degraded by the alkaline pH they encounter at the lower part of GIT.
- GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa.Particularly useful for the treatment of peptic ulcers caused by H. pylori infections.

Different Techniques Of Gastric Retention

Various techniques were used to encourage gastric retention of an oral dosage form

- High density systems:
- Floating Drug delivery systems
  - Non-Effervescent systems

    - Hydrodynamically balanced systems (HBS):

  - Effervescent systems

    - Gas generating Systems :
    - Low-density systems:
    - Raft systems incorporate alginate gels:
- Expandable Systems:
- Superporous Hydrogels
- Bioadhesive or mucoadhesive systems:
- Magnetic Systems

Among the available techniques from the formulation and technological point of view, the floating drug delivery system is considerably easy and logical approach.

1.5 FLOATING DRUG DELIVERY SYSTEMS

The concept of FDDS was described in the literature as early as 1962. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration

Formulation of this device must comply with the following criteria:

1. It must have sufficient structure to form a cohesive gel barrier.
2. It must maintain an overall specific gravity lower than that of gastric contents (1.004 –1.010).
3. It should dissolve slowly enough to serve as a drug reservoir.

Classification of floating drug delivery systems (FDDS)

Based on the mechanism of buoyancy, two distinctly different technologies, i.e. non effervescent and effervescent systems, have been utilized in the development of FDDS.

A. Effervescent Floating Dosage Forms

i) Gas Generating Systems

a) Intra Gastric Single Layer Floating Tablets or Hydro dynamically Balanced System (HBS): These are as shown in Fig.01 and formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

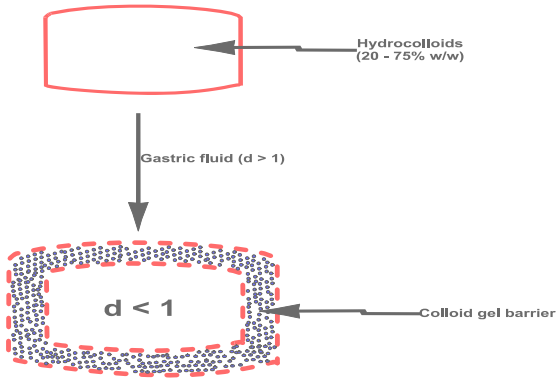
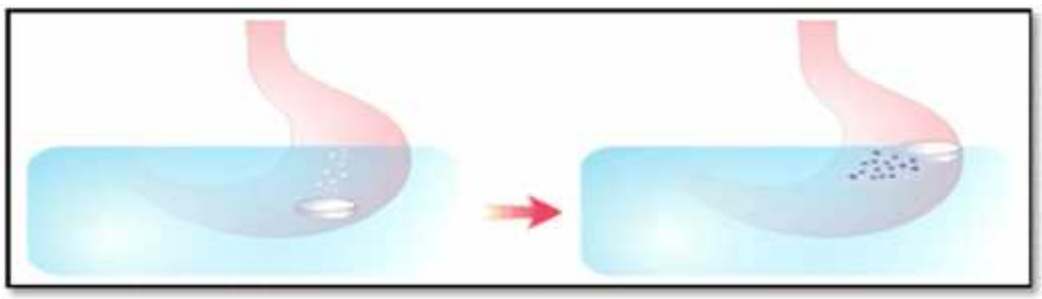


Fig 01: Intra Gastric Single Layer Buoyant Tablet.



b) Intra Gastric Bilayer Floating Tablets

These are also compressed tablet as shown in Fig 9 and containing two layers i.e.,

i. Immediate release layer and
ii. Sustained release layer.

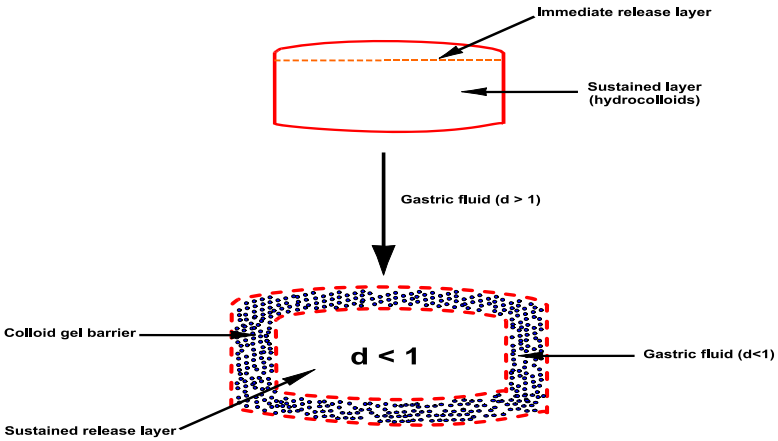


Fig 02: Intra Gastric Bilayer Buoyant Tablet.

c) Multiple Unit type floating pills

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layers consist of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the system.

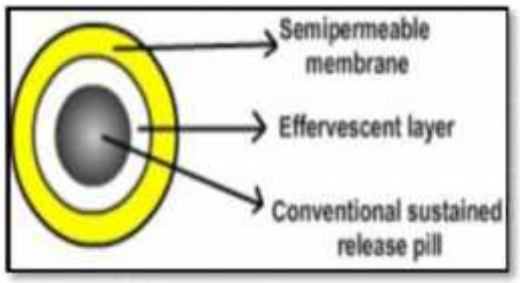


Fig 03: A multi-unit oral buoyant dosage system (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37^0C)

ii) Volatile Liquid / Vacuum Containing Systems

a) Intragastric Floating Gastrointestinal Drug Delivery System

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro porous compartment, as shown in Fig 04.

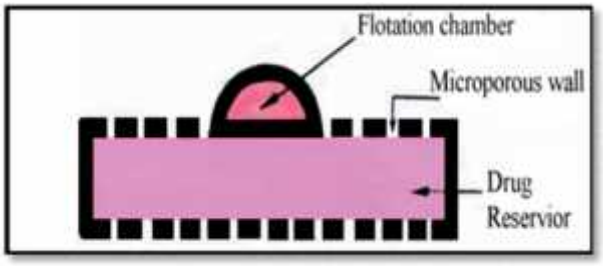


Fig 04: Intra Gastric Floating Gastrointestinal Drug Delivery Device

b) Inflatable Gastrointestinal Delivery Systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir.

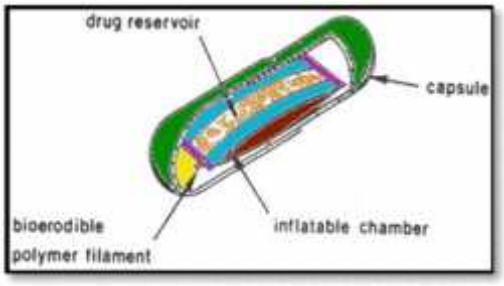


Fig 05: Inflatable Gastrointestinal Delivery System

After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid. This system is shown in Fig 05.

c) Intragastric Osmotically Controlled Drug Delivery System

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastirc osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The floating support is also made to contain a bio erodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach. This system is shown in Fig 06.

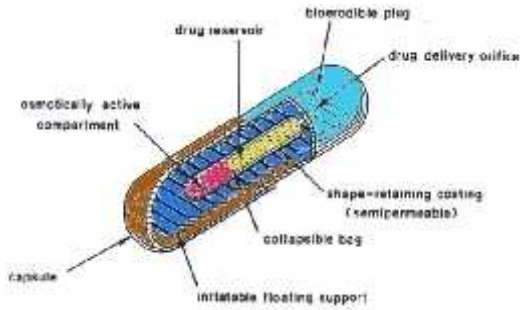


Fig 06: Intragastric Osmotically Controlled Drug Delivery System

iii) Raft-forming systems

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles (Fig. 6) on contact with gastric fluid. Formulations also typically contain antiacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment as with Liquid Gaviscon\ (GlaxoSmithkline).

B. NON-EFFERVESCENT SYSTEMS

The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as Polycarbonate, Polyacrylate, Polymethacrylate, polystyrene as well as bioadhesive polymer such as Chitosan and Carbopol. The various types of this system are as:

a) Single Layer Floating Tablets

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

b) Bilayer Floating Tablets

A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

c) Alginate Beads

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours.

d) Hollow Microspheres

Hollow microspheres (micro balloons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was

poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The micro balloons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*.

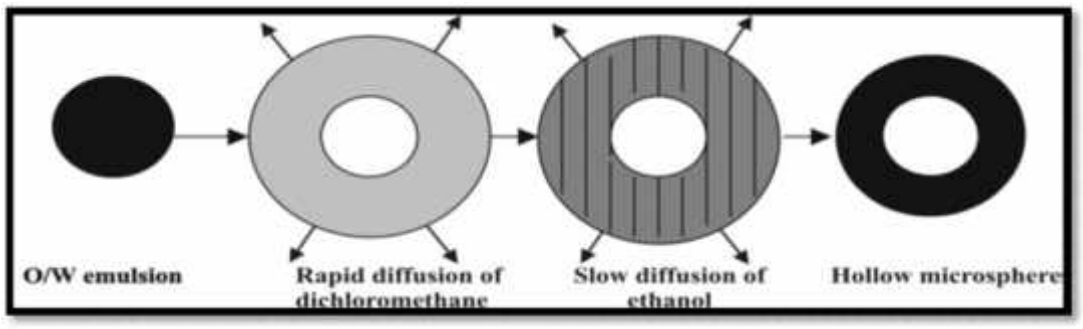


Fig 07: Hallow microspheres

1.6 BILAYER TABLETS

Multi - Layer Tablets

Layer tablets are composed of two or three layers of granulation compressed together. They have the appearance of a sandwich because the edges of each layer are exposed[13]. This dosage form has the advantages of separating two incompatible substances with an inert barrier between them and possibility of sustained- release from one portion. The weight of each layer can be accurately controlled, in contrast to putting one drug of a combination product in a sugar coating.. Coloring the separate layers provide many possibilities for unique tablets identity. Analytical work may be simplified by a separation of the layers prior to assay.

Bilayer Tablet is a new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system.these are the dosage forms having two active ingredients present as two distinct separate layers compressed into a tablet.

Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an

extended release manner. Bi-layer tablet is suitable for sequential release of two drugs in combination. To separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose.

Various Techniques for Bi Layer Tablet

A) OROS® push pull technology

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.

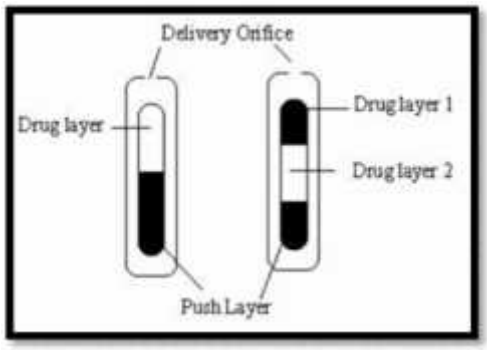


Fig no – 08: Bilayer and trilayer OROS Push pull technology

B) L-OROS tm technology

This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice.

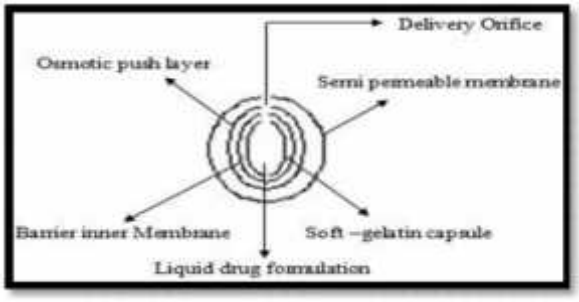


Figure 09: L – OROS tm technology

C) EN SO TROL Technology

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies

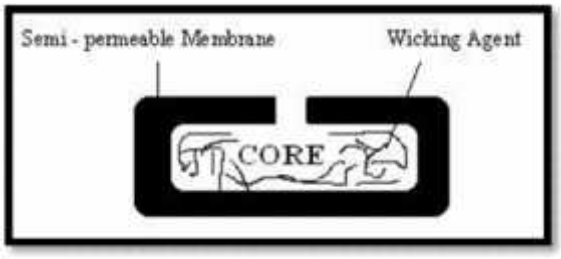
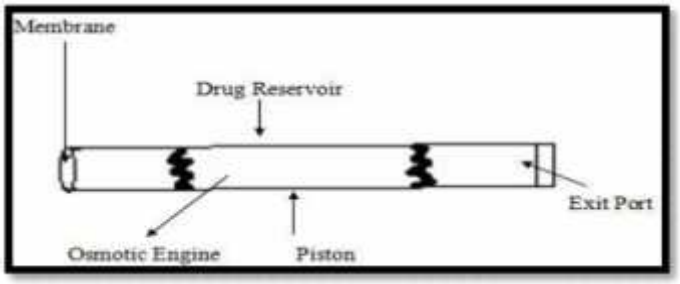


Figure 10 : EN SO TROL Technology

D) DUROS Technology

The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form in continues and consistent from over months or year.



E) Elan Drug Technologies' Dual Release Drug Delivery System

(DUREDAS™ Technology) is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tableting process can provide an immediate release granulate and a modified-release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers.

Benefits offered by the DUREDAS™ technology include

1) Bilayer tabletting technology.

2) Tailored release rate of two drug components.

3) Capability of two different CR formulations combined.

4) Capability for immediate release and modified release components in one tablet.

5) Unit dose tablet presentation

Bi-layer Tablets: Quality and GMP-Requirements

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of:

- ✓ Preventing capping and separation of the two individual layers that constitute the bi-layer tablet
- ✓ Providing sufficient tablet hardness
- ✓ Preventing cross-contamination between the two layers
- ✓ Producing a clear visual separation between the two layers
- ✓ High yield
- ✓ Accurate and individual weight control of the two layers these requirements seem obvious but are not as easily accomplished as this article aims to demonstrate

Limitations of The Single Sided Press Bi-Layer Tablets

- ❖ No weight monitoring/control of the individual Layers.
- ❖ No distinct visual separation between the two Layers.
- ❖ Very short first layer-dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems. This may be corrected by reducing the turret-rotation speed (to extend the dwell time) but with the consequence of lower tablet output.
- ❖ Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration to eliminate these limitations, a double-sided tablet press is preferred over a single-sided press. A double-sided press offers an individual fill station, pre -compression and main compression for each layer.

Different attempts made by scientists for preparation of bilayer formulations

- **Linhong *et al.,*** developed that the metformin hydrochloride has synergistic effect with glimepiride; the medicine comp has the advantage of reduced dose of each ingredient equivalent curative effect to single ingredient medicine and convenient administration.
- **Wagstaff et *al.,*** developed that the metformin is released at a controlled rate from a central osmotic tablet core through a semi permeable coating. A decrease in fasting plasma insulin, a marker of insulin resistance was seen with metformin extended release but not with immediate release. It shows that the metformin extended release given in the single dose is equal to the metformin immediate release given in the divided dose.
- **Chawla *et al.,*** developed the combination of the biguanide and a sulfonylurea. It provides the extended release of both the drugs i.e. Metformin and Glipizide.
- **Kesarwani *et al.,*** developed an oral solid dosage form that includes a combination of a biguanide as an extended release phase and a sulfonylurea as an immediate release coating form. A tablet was formulated which contains core material as metformin hydrochloride by using HPMC as a polymer ; seal coating; then coating of glimepiride by using HPMC as a polymer; then film coating was done.
- **Shanghvi *et al.,*** developed that spaced drug delivery system release two or more antidiabetic agents at different times after oral administration, for the treatment of diabetic mellitus. The delayed release metformin hydrochloride core prepared by granulation and compression of ingredients was mixed with the immediate release glipizide granules and encapsulated in hard gelatin capsules.
- **Amit Kumar *et al.,*** developed orally administrated extended release pharmaceutical compounds that include a combination of a highly water soluble high dose (i.e. 500 mg) biguanide (metformin hydrochloride)and a water insoluble low dose (2 mg) sulfonylurea in a extended release bilayered dosage form.

- **Tang *et al.,*** developed the metformin and glimepiride which can decrease free fatty acid levels, body weight index, blood glucose and insulin resistance. Free fatty level can reflect the index of insulin resistance to some degree.

1.7 Hydrophilic Polymers In Controlled Drug Delivery

The prototypes of orally administered hydrophilic matrices were first described more than 4 decades ago, and since then, a number of ER technologies have been developed and registered. From a commercial perspective, hydrophilic matrices are economical to develop and manufacture due to the use of available equipment without further investment, stable formulations, and broad regulatory acceptance. In most instances, hydrophilic matrices use polymers with flexible chemistry that offer an opportunity to formulate an ER dosage form for a wide range of APIs with varying solubility and doses.

Various high molecular weight, water soluble or water-swellable polymers have been used in hydrophilic matrices, such as Hypromellose [hydroxypropyl methylcellulos, HPMC], Hydroxyl propyl cellulose, Sodium carboxy methyl cellulose, Sodium alginate, Carbomers, and Polyethylene oxide

HPMC, by far, is the most popular polymer in matrix applications because of its ability to obtain desired release profiles for a wide range of drugs, provide robust formulation, global availability, cost-effective manufacture, broad regulatory acceptance, and extensive history on its use.

Although the use of HPMC as a rate controlling hydrophilic polymer in ER formulations is well-documented, the following are still some unmet needs and challenges associated with ER hydrophilic matrices:

- HPMC is a nonionic polymer and hence the matrices exhibit pH independent drug release profiles when drug solubility is pH independent. However, when drug solubility is pH-dependent, eg, for Superdisintegrants : HPMC matrices may exhibit an initial burst release for very soluble drugs.This behavior has been attributed to the rapid dissolution of the drug from the surface and near the surface of the matrix, while the polymer undergoes hydration to form a protective gel layer.

- Developing an ER hydrophilic matrix formulation of high dose APIs (eg 500 to 1000 mg) is challenging because of overall restrictions on size of the tablets for ease of swallowing.
- ER hydrophilic matrix formulations of very slightly soluble or practically insoluble drugs may exhibit food effects, ie, variable bioavailability, depending on administration during fasting or fed state.

COMBINATION OF HPMC WITH OTHER POLYMERS

HPMC is a nonionic water soluble polymer, and hence, the possibility of chemical interaction or complexation with other formulation components is greatly reduced, and the hydration and gel formation of its matrices are pH-independent. Thus HPMC is typically used as the primary polymer, and other approved polymer(s) have been added to enhance functionality and as a tool to modulate the drug release profile. Here, blends of HPMC with other polymers, including ionic, nonionic, and water-insoluble polymers, are discussed.

Drug solubility is an important factor determining the mechanism of drug release from HPMC hydrophilic matrices. Practically insoluble drugs (Eg, solubility < 0.01 mg/mL) may dissolve slowly and have slow diffusion through the gel layer of a hydrophilic matrix. Therefore, the main mechanism of release would be through surface erosion of the hydrated matrix. In these cases, the control over matrix erosion to achieve consistent ER throughout the GI tract is critical, hence, low viscosity grades of HPMC (Eg, METHOCEL Premium K100LV or E50LV) that provide adequate erosion are recommended.

For drugs with very high water solubility, the drug dissolves within the gel layer (even with small amounts of free water) and diffuses out into the media. Therefore, it is important to ensure integrity of the gel layer after the drug has been dissolved and released from the gel layer. In this case, it is critical to have a strong gel layer through which diffusion can occur and hence, high viscosity grades of HPMC (METHOCEL Premium K4M, K15M, or K100M) are recommended in their formulations.

The strategy of blending high- and low viscosity grades of HPMC has also been reported for achieving the zero-order release profile from matrix formulations and for reducing the drug release variability (low % Relative Standard Deviation, % RSD), thereby providing more uniform clinical levels of the drug.

HPMC With Poly Methacrylates

Combination of HPMC and poly methacrylates, most notably anionic polymers (Eudragit L100 55) in hydrophilic matrices, has been reported for developing pH-independent release profiles for weakly basic drugs. Combining of Eudragit E 100 with HPMC matrices has been shown to result in pH-independent release for acidic drugs, such as Divalproex sodium. This effect has been attributed to the enhanced solubility and hence, release of the drug in acidic media and retardation of the drug release in basic media.

HPMC With Poly Vinyl Acetate Phthalate

Poly Vinyl Acetate Phthalate is another enteric polymer used in combination with HPMC to control the micro enviornmental pH and enhance matrix properties, such as gel strength and erosion. Combining PVAP with HPMC to formulate matrices containing verapamil hydrochloride (Hcl) has been reported. slower drug release was observed for blends of HPMC and PVAP compositions as compared to the single HPMC polymer matrix.

HPMC With Sodium Alginate

Sodium alginate has also been used Within HPMC matrices to obtain a pH independent release profile for basic drugs. It has been reported that at low pH (in gastric environment), sodium alginate precipitates in the hydrated gel layer as alginic acid. This alginic acid then provides a firm structure to the gel and retards rate of erosion. Solubility of basic drugs at this pH is high, hence diffusion through the matrix gel layer predominates as a mechanism of drug release. There are commercially available ER matrices using the combination of HPMC and sodium alginate.

HPMC With Sodium Carboxy Methyl Cellulose (NaCMC)

Sodium Carboxy Methyl Cellulose (NaCMC) has been reported to have synergistic hydrogen-bonding interactions with HPMC. Combining HPMC with Na CMC may result into zero-order release profiles for the drugs Propranolol Hydrochloride, Metoprolol Tartrate, Oxprenolol Hydrochloride, and Alprenolol Hydrochloride. However, it was later confirmed that enhancement in viscosity was not solely responsible for modulating the drug release profile, but that the complex formation between the anionic polymer and cationic drug also played an important role. Freely soluble cationic drugs have been reported to be released slower from combinations of HPMC and Na CMC matrices than when formulated with HPMC alone, an effect attributed to drug/polymer interaction.

HPMC With Xanthan Gum

Combination of HPMC with xanthan gum has been reported to result in greater retardation in drug release profile compared to single polymer systems. Rapid hydration of xanthan gum combined with firm gel strength of HPMC have been attributed to slower drug release of high-solubility APIs. In this system, the initial burst release, which is typical of highly soluble drugs, was controlled by rapid hydration of xanthan gum, whereas subsequent drug release and matrix integrity were maintained by the firm gel of HPMC.

HPMC & FATTY ACIDS, ALCOHOLS, OR WAXES

Combinations of HPMC and fatty acids, alcohols, or waxes have been reported with varied degrees of success.49,50 Low-melting lipophilic materials blended at low concentrations (≤ 7.5% w/w) with HPMC have shown potential in achieving the ER of Metformin, a highly solubile active, suggesting the possibility of niche applications for such matrix blends.49 When used at high concentrations, because of their low melting points, fatty acids or waxes may enable processing of HPMC formulations by melt granulation.

HPMC & NON IONIC HYDROPHILIC POLYMERS

HPMC and poly ethylene oxide [PEO] has been used for modulating drug release and to prevent the burst release of highly soluble APIs. In addition, the high-swelling capacity of PEO has been used in HPMC matrices to achieve expanded swelling, resulting in enhanced gastro-retention of the dosage form. Combination of HPMC and HPC in the matrix system has been reported to provide retardation in the drug release profiles compared to single polymer systems. This retardation has been attributed to a stronger gel layer of the resultant matrix, reducing diffusion and erosion rate characteristics of the gel layer.

Challenges With Hydrophilic Matrix System

In spite of the presence of numerous products in the marketplace, there are still some challenges associated with hydrophilic matrix systems,

- ✓ Potential burst release with high solubility APIs.
- ✓ Size limitations for high dose APIs.
- ✓ Potential food effect, and obtaining ph independent release profiles for drugs that Show ph-dependent solubility.
- ✓ Developing new polymeric excipients to overcome these challenges remains limited due to the regulatory constraints, cost, and establishing safety and market acceptability
- ✓ It was shown that blends of pharmaceutically approved polymeric excipients have been a powerful strategy to achieve and optimize desired drug release characteristics and product performance.

1.8 IMMEDIATE RELEASE TABLETS

In many cases, the disintegration time of solid dosage forms is too long to provide appropriate therapeutic effect. Therefore the disintegration time of the tablets can be decreased by formulating immediate release tablets. Tablets for

immediate release often consist of filler, a binder, lubricants and disintegrants. To improve the disintegration time, so-called disintegrants are used.

The most accepted mechanisms of their action are wicking, swelling, deformation recovery and particle repulsion. Together, these phenomena create a disintegrating force within the matrix. In the past, non-modified disintegrants were used to accelerate disintegration, that is, alginates, starches, ambrelite resins, cellulosic materials, pectines and others. Today, a fast working superdisintegrants were chemically modified, typically by crosslinking the organic chains of a polymeric molecules.

Superdisintegrants

Three classes of superdisintegrants are commonly used: modified cellulose (croscarmellose sodium - Ac-Di-Sol®, Vivasol®), crosslinked polyvinyl-lpyrrolidone (Polyplasdone® XL-10) and modified starch (Sodium Starch Glycolate – Primojel®, Explotab®).

Mechanism Of Superdisintegrants

The tablet breaks to primary particles by one or more of the mechanisms listed below.

1. Because of Heat of Wetting (Air Expansion):

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and can not describe the action of most modern disintegrating agents.

2. Swelling: Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

3. Porosity and Capillary Action (Wicking):

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

4. Due To Disintegrating Particle/Particle Repulsive Forces:

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

5. Due To Deformation:

During tablet compression, disintegranted particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a break up of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

6. Due To Release of Gases:

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in

humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

Table showing properties of important superdisintegrants used in the study

S no	Superdisintegrant	properties
1	Cros carmellose sodium	High swelling capacity, effective at low concentration (0.5-2.0%), can be used up to 5%
2	Crospovidone	Completely insoluble in water. Rapidly disperses and swells in water, but does not gel even after prolonged exposure. Greatest rate of swelling compared to other disintegrants. Greater surface area to volume ratio than other disintegrants. Effective concentration (1-3%). Available in micronized grades if needed for improving state of dispersion in the powder blend.
3	Sodium starch glycolate	Absorbs water rapidly, resulting in swelling up to 6%. High concentration causes gelling and loss of disintegration

Table Showing Various Superdisintegrants and Their Applications.

Superdisintegrants and Disintegrants			Applications			
Brand Name	Common Name	Classification	Functional Category	Properties	EMC at 25°C/ 90%RH	Typical Uses
CL-Kollidon	Crospovidone	Polyvinyl-pyrroidone	Tablet super disintegrant	Swelling (18% in 10s), (45% in 20s)	60%	Disintegrant (Dry and Wet granulation)
Ac-DiSol	Croscarmellose Sodium	Cellulose, carboxymethyl ether, sodium salt crosslinked	Tablet and capsule disintegrant	Wicking and swelling (12% in 10s), (23% in 20s)	88%	Disintegrant for capsules, tablets and granules
Explotab Primojel	Sodium starch glycolate	Sodium carboxymethyl starch	Tablet and capsule super disintegrant	Swelling capacity (300 times)	–	Disintegrant (Dry and Wet granulation)
Explotab VI7	Sodium starch glycolate	(Cross linked substituted carboxymethyl ether) sodium carboxymethyl starch	Super disintegrant	More swelling than Explotab	–	Disintegration and dissolution aid. Not for use in wet granulation
Explotab CLV	Sodium starch glycolate	(Cross linked low substituted carboxymethyl ether)Sodium carboxymethyl starch	Super disintegrant	Swelling	–	Use in wet granulation and high shear equipment
L-HPC	Hycroxypropyl cellulose(low substituted)	Cellulose, 2-hydroxypropyl ether	Tablet and capsule super disintegrant	Swelling (13% in 10s), (50% in 20s)	37%	Disintegrant and Binder in wet granulation
Amberlite IRP88	Polacrilin Potassium	Cation exchange resin	Diluent and disintegrant	Swelling		Disintegrant
Starch 1500	Starch, pregelatinized	Pregelatinized starch	Diluent, binder and disintegrant	Hygroscopic	23%	Binder diluent and disintegrant
Avicel	Microcrystalline cellulose	Cellulose	Tablet and capsule diluent, Tablet disintegrant	Hygroscopic, swelling-(12% in 10s), (18% in 20s)	18%	Binder/diluent, lubricant and disintegrant

2. LITERATURE REVIEW

Fiona Palmer *et al*[1]., Investigated the effect of Hypromellose on Direct Compression of Metformin HCl 500mg to form an Extended Release Formulation Extended release (ER) formulation of metformin hydrochloride (HCl) presents the formulator with significant challenges due to its poor inherent compressibility, high dose and high water solubility. This study investigates the possibility for development of a direct compression ER matrix tablet using hypromellose by taking different ratios of Methocel K4M CR, Methocel K100M CR, 30%w/w inclusion of the controlled release polymer in the formula resulted in drug release profile similar to the Glucophage XR (500mg) tablet.

Basawaraj S. Patil *et al*[2]., Prepared Fast dissolving tablets (FDT) of Granisetron hydrochloride by direct compression method by incorporating superdisintegrants croscarmellose sodium and crospovidone in different concentrations (2.5, 5, 7.5 and 10 mg). The formulation GCS4 containing croscarmellose sodium showed superior in vitro dispersion time and drug release, as compared to other formulations. GCS4 tablet showed good dissolution efficiency and rapid dissolution. The 50% and 90% of drug release of tablet GCS4, was found within 0.45 and 2.59 min.

Praveen Nasa *et al*[3]., Formulated and characterized a floating drug delivery system, using Methocel K100M and E50.for Metformin hydrochloride by wet granulation method. The two grades were evaluated for their gel forming properties It was concluded that the formulation F5 (containing 160 mg of Methocel K100M and 40 mg of Methocel E50) was the optimum formulation amongst all the test batches. It may also be concluded from the investigation that a combination of Methocel K100M and Methocel E50 in the ratio of 4:1 may be satisfactorily employed in the formulation of a floating drug delivery system.

Durga Prasad Pattanayak *et al*[4]., The present research work was an attempt to design a formulation to improve the oral therapeutic efficacy with optimal control of

plasma drug level which contains two antidiabetic drugs i.e Metformin HCl and Glimepiride. a common analytical method for quantitative combined drug estimation was employed and evaluated. Two different matrix formulations were developed, one matrix layer with hydrophilic swellable polymer HPMC and another with hydrophobic polymer PEO as carriers for sustained drug delivery from matrices and were evaluated.

Lian-Dong Hu *et al*[5]., In this study, metformin hydrochloride (MH) sustained-release pellets were successfully prepared by centrifugal granulation. Seed cores preparation, drug layering, talc modification and coating of polymeric suspensions were carried out in a centrifugal granulator. After using Eudragit NE30D alone and a blend of Eudragit_ L30D-55/Eudragit_ NE30D (1:20)for coating, three kinds of sustained-release pellets with different formulations were obtained. The in vivo bioavailability showed varying sustained-release characteristics for the coated pellets when compared with IR MH tablets.

Sachin S. Kale *et al*[6]., Mentioned that Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system.. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. In the case of bilayered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper nonadhesive layer its delivery occurs into the whole oral cavity.

Sandip B. Tiwari *et al* [7]., In the post Hatch-Waxman Act 1984 era, developing an extended release (ER) formulation of a new chemical entity with extended patent life has become very crucial to innovator companies.. Hydrophilic matrix systems have been widely studied and accepted as an ER approach for oral drug delivery, It was shown that blends of pharmaceutically approved polymeric excipients have been a powerful strategy to achieve and optimize desired drug release characteristics and product performance. Combinations of HPMC with ionic and nonionic polymers have

been used in hydrophilic matrices to modulate the release profile and overcome some or all of the challenges observed with hydrophilic matrices.

Suvakanta dash *et al* [8]., In this paper they reviewed the mathematical models used to determine the kinetics of drug release from drug delivery systems. The quantitative analysis of the values obtained in dissolution/release rates is easier when mathematical formulae are used to describe the process. The mathematical modeling can ultimately help to optimize the design of a therapeutic device to yield information on the efficacy of various release models.

Ganesh Rajput *et al* [9]., The present investigation is aimed to formulate floating tablets of metformin hydrochloride using an effervescent approach for gastroretentive drug delivery system. Floating tablets were prepared using directly compressible method using polymers HPMC K 100M and HPMC K 4M for their gel-forming properties. It was concluded that polymer viscosity had major influence on drug release from hydrophilic matrix tablets as well as on floating lag time. The different ratios of HPMC K 4M and HPMC K 100M were evaluated to achieve apparent viscosity to 66633 cps. The optimized batch showed the highest f2=82 value, it contained 37.34mg of HPMC K 4M and 212.66mg of HPMC K100M.

M. M. Varma *et al* [10]., Sustained release gastroretentive dosage forms enable prolonged and continuous input of the drug to the upper parts of gastrointestinal tract. Gastroretentive floating drug delivery systems (GFDDS) of metformin hydrochloride, an antidiabetic drug with an oral bioavailability only 50%(because of its poor absorption from lower gastrointestinal tract) have been designed and evaluated. Hydroxy propyl methyl cellulose(HPMC K4M) and carbopol 934P were used as polymers and sodium bicarbonate as gas generating agent to reduce floating lag time.The in vitro drug release followed first order kinetics and drug release was found to be diffusion controlled.

K. Gupta *et al* [11]., A simple, precise and highly selective analytical method was developed for simultaneous estimation of Metformin HCl and Sitagliptin in tablet formulation. Estimation was carried out by multi-component mode of analysis at selected wavelength of 232 nm and 267 nm for Metformin HCl and Sitagliptin respectively in distilled water. The method was found to be linear in the range of 1-40 µg/ml and accuracy of the method was confirmed by recovery studies of tablet dosages forms and was found to be 99.35% and 98.33% for Metformin HCl and Sitagliptin respectively. % concentration of Metformin HCl and Sitagliptin in marketed formulation was found to be 98.26% ± 0.29 and 97.35% ± 1.38 respectively. The values of precision and robustness lie within acceptable limit.

N.N.Rajendran *et al* [12]., The present study was to establish Bi-layer tablets containing Metformin HCl as sustained release and Pioglitazone HCl as immediate release layer. immediate release layer were prepared by direct compression method using superdisintegrants such as sodium starch glycolate and crosscarmellose sodium. All the values were found to be within limit. The result showed that combinations of polymers namely HPMC K100M and HPMC K4M in sustained layer can control the release of drug. The *in vitro* release profiles follows Higuchi's equation as the plots showed high linearity (R2 >0.988) and diffusion was the mechanism of drug release. The formulations (P6M7) having immediate release layer produces immediate effect within 54 second followed by sustained release (97.35%) at 8 hrs and it comparable with innovator.

Shubhangi B. Bagde *et al* [13]., In the present investigation an attempt was made to reduce the dose frequency, to prevent nocturnal heart attack and to improve the patient compliance by developing a Bilayer tablet having extended release (ER) layer of Metoprolol succinate and immediate release(IR) layer of Ramipril. Hydroxylpropylmethylcellulose K100M and Sodium Carboxymethylcellulose was used for extended release of Metoprolol succinate. Among the Ten formulations, F_{10} showed compliance with US pharmacopoeial standards, extend the release of drug for 20 hours

with 99.6% drug release and subjected to stability studies for 1 month at 40 ^{0}C/75% RH.

Himansu Bhusan Samal *et al* [14]., The investigation was concerned with design and characterization of oral Sustained release matrix tablets of Zidovudine (AZT) in order to improve efficacy and better patient compliance. Matrix tablets were prepared by Wet granulation method using various proportions of hydrophilic polymers like Sodium CMC, HPMC, Eudragit-L155, & Xanthan gum along or in combination with hydrophobic polymer ethyl cellulose. From the above study it was concluded that presence of sodium CMC gives zero-order release kinetics and the linearity ranges from 0.990 to 0.996. It has also good drug entrapment efficiency ranges from 96 to 106% of drug. Formulation containing sodium CMC with Xanthan gum and EC gives sustained release of drug more than 12hrs.

Subas C. Dinda *et al* [15]., The objective of the present study is to formulate a fixed dose combined drug formulation of valsartan (VAL) as an immediate release layer and metformin HCl (MHCl) as a sustained release form using bilayer tablet technology, which enables biphasic drug release for once daily dosing to get a better therapeutic efficacy. The immediate release layer was prepared using super disintegrant crospovidone and extended release layer using hydroxypropylmethylcellulose (HPMC K100M), sodium carboxy methyl cellulose and povidone K90.

Honey Goel *et al* [16]., Orally disintegrating systems have carved a niche amongst the oral drug delivery systems due to the highest component of compliance they enjoy in patients especially the geriatrics and pediatrics. In addition, patients suffering from dysphagia, motion sickness, repeated emesis and mental disorders prefer these medications because they cannot swallow large quantity of water. Further, drugs exhibiting satisfactory absorption from the oral mucosa or intended for immediate pharmacological action can be advantageously formulated in these dosage forms. A variety of dosage forms like tablets, films, wafers, chewing gums, microparticles,

nanoparticles etc. have been developed for enhancing the performance attributes in the orally disintegrating systems

Bala Sekaran.C *et al* [17]., A simple, sensitive and reproducible spectrophotometric method was developed for the determination of sitagliptin phosphate in bulk and in pharmaceutical formulations. The proposed method is based on condensation of the primary amino group of sitagliptin phosphate with acetyl acetone and formaldehyde producing a yellow colored product, which is measured spectrophotometrically at 430nm. Beer's law is obeyed over a concentration range of 5-25 µg/ml. No interference was observed in the presence of common pharmaceutical excipients. The validity of the method was tested by analyzing sitagliptin phosphate in its pharmaceutical preparations.

S.B Shirsand *et al* [18]., In the present study, novel co-processed superdisintegrants were developed by solvent evaporation method using crospovidone and croscarmellose sodium in the different ratios (1:1, 1:2 & 1:3) for use in the fast dissolving tablet formulations. Fast dissolving tablets of metoclopramide hydrochloride were prepared using the above co-processed superdisintegrants. Among the designed formulations, the formulation (CP1) containing 4% w/w of co-processed superdisintegrant (1:1 mixture of crospovidone and croscarmellose sodium) emerged as the overall best formulation (t50% 2.4 min) based on drug release characteristics in pH 6.8 phosphate buffer compared to commercial conventional tablet formulation (t50% 6 min).

Jonathan K Reynolds[19]., JanumetTM, a fixed dose combination of sitagliptin/metformin HCL manufactured by Merck Pharmaceuticals, has received US Food and Drug Administration approval for treatment of patients with type 2 diabetes, that are inadequately controlled, either by sitagliptin or metformin alone or together in free-dose combination form. Sitagliptin, an inhibitor of the enzyme DDP-4, assists patients with type 2 diabetes mellitus to achieve glycemic control. It has been shown to be safe and effective at 100 mg daily doses. The effect of giving sitagliptin in

combination with metformin is thought to have a complimentary and possibly additive effect on glycemic control.

Eytan A. Klausner *et al* [20]., These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their gastric retention time (GRT). After drug release, their dimensions are minimized with subsequent evacuation from the stomach. Gastroretentivity is enhanced by the combination of substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach.. Narrow absorption window drugs compounded in such systems have improved in vivo absorption properties. The current review deals with expandable GRDFs reported in articles and patents, and describes the physiological basis of their design.

Madhusudan Rao Yamsani *et al* [21]., The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. One of the most feasible approaches for achieving a prolonged and predictable dug delivery profiles in the gastrointestinal tract is to control the gastric residence time, using gastroretentive dosage forms that will provide us with new and important therapeutic options. From the formulation and technological point of view, the floating drug delivery system is considerably easy and logical approach.

A Ramachandran *et al* [22]., The prevalence of diabetes is rising all over the world due to population growth, aging, urbanisation and an increase of obesity and physical inactivity. The International Diabetes Federation (IDF) estimates the total number of people in India with diabetes to be around 50.8 million in 2010, rising to 87.0 million by 2030. The primary goal in the management of diabetes mellitus is the attainment of near-normal glycaemia. Glucagon-like peptide-1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-4) are novel agents that show promising results. Exenatide is the first in the incretin mimetic class and liraglutide is a once-daily human GLP-1 analogue.

3. SCOPE AND OBJECTIVE

3.1 Scope of the work

Diabetes is one of the most prevailing and advancing diseases in the world having affected 6.6% of the world population [22]. Metformin hydrochloride is the most widely used Oral Anti Diabetic drug in the world. Metfromin shows high aqueous solubility and low cell membrane permeability. The usual dosage for Metformin is 250–500 mg 3-4 times daily, up to a maximal of 2.5 g/day. The absolute bioavailability of Metformin hydrochloride is 50–60% and is having short biological half-life of 6.2 hrs.

The use of Metformin therapy has the high incidence of gastrointestinal side effects. Frequent dosing schedule leading to high GI side effects and high daily dose makes its use unsuccessful, thus it is reasonable to formulate sustained release Metformin tablets to prolong its duration of action and to reduce total dose of drug administered as well as the incidence of adverse side effects, thus improving the patient compliance.

A conventional oral sustained release formulation release most of the drug content at colon. Since Metformin has absorption window in stomach & upper part of GIT up to intestine, there is a need to develop gastro retentive sustained release formulation which, In contrast to conventional extended-release Metformin tablets reported in the literature gives extended plasma concentration time profiles, increased bioavailability with lower C max and greater T max [10].

The combination of a DPP-4 Inhibitor with Metformin allows a broad and complementary spectrum of anti diabetic actions. This combination does not increase the risk of hypoglycemia, do not promote weight gain, and do not cause adverse effect caused by various other oral anti diabetic combinations. Both the drugs have a *complimentary and possibly additive effect on glycemic control and reduced glycosylated haemoglobin (HbA(1c)) levels* [22].

Bi-layer tablet is suitable for sequential release of two drugs in combination, separating two incompatible substances. Typically an immediate release granulate is

first compressed followed by the addition of a controlled release element which is compressed onto the initial tablet, this gives the characteristic Bi-layer effect to the final dosage form. In the case of bi-layered tablets drug release can be rendered almost unidirectional [6].

HPMC is the mostly used nonionic water soluble polymer showing pH independent and desired drug release profiles for a wide range of drugs, provide robust formulation, global availability, cost-effective manufacture. HPMC is typically used as the primary polymer, and other approved polymer(s) have been added to enhance functionality and as a tool to modulate the drug release profile [7].

Sodium Carboxy Methyl Cellulose (Na CMC) has been reported to have synergistic hydrogen-bonding interactions with HPMC [7]. Freely soluble cationic drugs have been reported to be released slower from combinations of HPMC and Na CMC matrices than when formulated with HPMC alone.

Superdisintegrants are the agents that promote fast disintegration of the tablets by increasing water penetration and dispersion of the matrix [16]. Here, in this study cross povidone, croscarmellose sodium, sodium starch glycolate were used a superdisintegrants and were evaluated for their effect on dissolution and disintegration of Sitagliptin layer. Fixed dose combinations (or) combination therapy (Two or more active ingredients in one dosage form) offer several advantages such as lower cost, improved efficacy, better compliance as number of doses/ pills per day decreases, and fewer side effects. Thus currently focus is shifting fast to fixed dose combinations in the form of bi layer (or) multi layer dosage forms to treat diseases like Diabetes, Hypertension, Tuberculosis, HIV etc

3.2 Objective of the Work

The main objective of present study is to develop a dosage form which provides fixed dose combination therapy for the treatment of NIDDM. Since the combination of Metformin Hcl and Sitagliptin shows complimentary and possibly additive effect on glycemic control and reduced glycosylated haemoglobin (HbA(1c)) levels with no weight gain and reduced side effects.

The objectives of the present study are:

1. To improve the Bioavailability of Metformin by formulating as floating SR layer.
2. To reduce the dose, dosage frequency, dose related side effects and number of tablets per day by formulating Metformin and Sitagliptin as Bilayer tablets.
3. To study the effect of different concentrations of hydrophilic polymers like HPMC K100 M and Sodium CMC on release of Metformin .
4. To study the effect of different Superdisintegrants on drug release pattern from the immediate release layer.
5. To study the effect of different concentrations of sodium bi-carbonate on floating behavior.
6. To investigate the mechanism of release of Metformin from SR layer.

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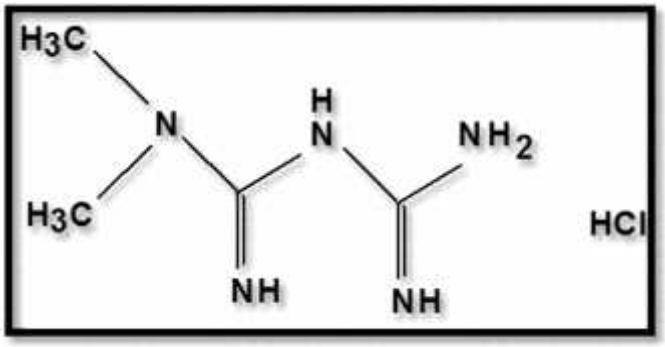
4.2 DRUG PROFILE

METFORMIN HYDROCHLORIDE [52, 54]

Structure



Chemical Name	**:**	1-carbamimidamido-N,N-dimethylmethanimidamide
Empirical Formula	**:**	$C_4H_{11}N_5$.HCl
Molecular Weight	**:**	165.62
Melting Point	**:**	222 to 226 ^oC
Category	**:**	Hypoglycemic agent
Dose	**:**	0.5 to 3 g daily, in divided doses [35]
PKa	**:**	12.4
p^H	**:**	pH of 1% aqueous solution of drugs is 6.68
Description	**:**	White, crystalline powder, hygroscopic which is odor less and has a bitter taste.

Appearance, odor and Color **:** Metformin HCl is a white, hygroscopic powder,

Solubility: Freely soluble in water, slightly soluble in ethanol (95%), practically insoluble in acetone, chloroform, dichloromethane and ether.

Pharmacokinetics:

Absorption: It is a BCS class III (highly soluble- poorly permeable) drug. The absolute bioavailability under fasting conditions is approximately 50-60%. It is absorbed mainly from the upper part of small intestine. There is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases and slightly delays the absorption of metformin.

Distribution: The apparent volume of distribution (V_d) of metformin is 654 liters. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. At usual clinical doses and dosing schedules, steady state plasma concentrations of metformin reached within 24-48 hours and are generally less than 1 µg/ml.

Metabolism And Elimination: Metformin is excreted unchanged in the urine and neither undergo hepatic metabolism, nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 3 hours. Duration of action is 8-12 hours.

Dosage and Administration:

The usual effective dosage of metformin hydrochloride is 1500- 2550 mg/day given in divided doses. It is commercially available in tablets of 500 mg or 850 mg immediate release and 500 mg and 1000 mg extended release tablets.

There is no fixed regimen for the management of hyperglycemia in patients with type II diabetes. Dosage must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose. The maximum recommended daily dose of extended release tablet in adult is 2500 mg.

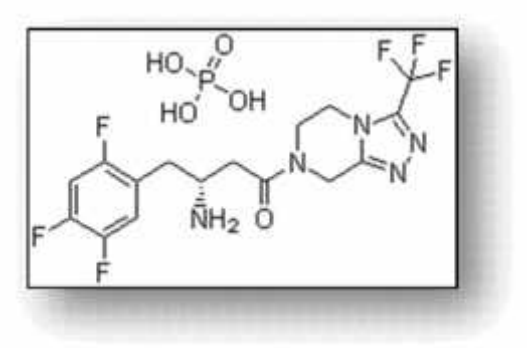
Adverse Effects:

Approximately 30% of patients may have gastrointestinal adverse effects, such as diarrhoea, nausea, epigastric discomfort, and anorexia. Gastrointestinal side

effects are commonly dose related; gradually increasing the dosage. Taking doses with food or temporarily reducing the dosage may help avoid these reactions. The most worrisome adverse effect of metformin is lactic acidosis

SITAGLIPTIN PHOSPHATE [53]:

Structure:



Chemical Name : 4-Oxo-4-(3-(trifluoromethyl)-5,6dihydro(1,2,4)triazolo[4,3 a]pyrazin-7(8H)-yl)-1-(2,4,5-trifluorophenyl)butan-2-amine phosphate

Empirical Formula : $C_{16}H_{15}F_6N_5O \cdot H_3PO_4$

Molecular Weight : 505.31

Melting Point : 198 - 202 C

Category : Hypoglycemic agent DPP-4 inhibitor.

Dose : 25 to 100 mg daily, in divided doses or once daily.

PKa : 12.4

p^H : pH of 1% aqueous solution of drugs is 6.68

Description : white to off-white crystalline powder

Solubility: Freely soluble in water, slightly soluble in ethanol (95%), practically insoluble in acetone, chloroform, dichloromethane and ether.

Pharmacokinetics:

Absorption: It is a BCS class I (highly soluble- highly permeable) drug. Rapidly absorbed following oral administration, with an absolute bioavailability of 87%

Distribution: The apparent volume of distribution (V_d) of metformin is 198 L [healthy subjects]. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Metabolism And Elimination: Sitagliptin does not undergo extensive metabolism. In vitro studies indicate that the primary enzyme responsible for the limited metabolism of Sitagliptin was CYP3A4 (oxidation), with contribution from CYP2C8. Approximately 79% of Sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. Elimination of Sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Half life is 12.4 hours.

Mechanism of Action:

Sitagliptin is a highly selective DPP-4 inhibitor, thereby increasing the concentration and prolonging the action of incretin hormones like glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are generally inactivated by the enzyme, DPP-4.

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4.2 EXCIPIENT PROFILE

HYDROXY PROPYL METHYL CELLULOSE [46]:

Non-Proprietary Names:

BP: Hypromellose JP: Hydroxypropylmethylcellulose

PhEur: Hypromellosum USP: Hypromellose

Synonyms: Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

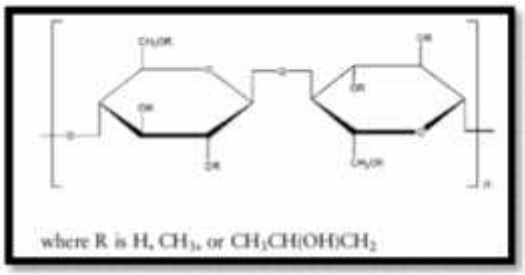
Chemical Name : Cellulose hydroxypropyl methyl ether [9004-65-3]

Empirical Formula: C8H15O6 – (C10H18O6)n – C8H15O5 Molecular weight is approximately 10 000–1 500 000.

Description:

Hypromellose is an odorless and tasteless, white or creamywhite fibrous or granular powder

Structural Formula:



Functional Category:

Coating agent, film-former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

Density: 0.25 – 0.70 g/cm3

Solubility:

Soluble in cold water forming a viscous colloidal solution. practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol.

Melting point: Browns at 190–2008C. Chars at 225–2308C. Glass transition temperature is 170–1808C.

Moisture content:

Hypromellose absorbs moisture from the atmosphere. The amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

Viscosity:

A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan- 2-ol provided the alcohol content is less than 50% w/w.

Safety:

It is widely used in many oral and topical pharmaceutical formulations. It is generally regarded as a non-toxic and non-irritant material, although excessive consumption may have laxative effect**.**

Pharmaceutical Applications:

- Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations
- In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.

- Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.

SODIUM CARBOXY METHYL CELLULOSE[46]

Nonproprietary Names:

BP: Carmellose sodium JP: Carmellose sodium

PhEur: Carmellosum natricum USP: Carboxymethylcellulose sodium

Synonyms:

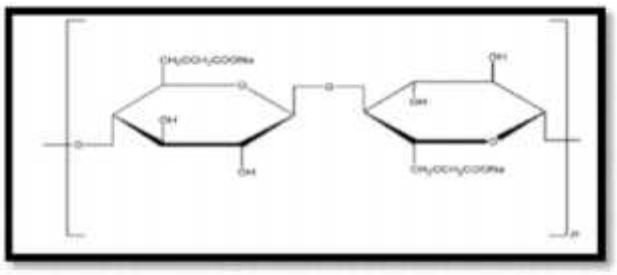
Akucell; Aquasorb; Blanose; cellulose gum; CMC sodium; E466; Finnfix; Nymcel; SCMC; sodium carboxymethylcellulose; sodium cellulose glycolate; sodium CMC; Tylose CB.

Chemical Name : Cellulose, carboxymethyl ether, sodium salt [9004-32-4]

Empirical Formula and Molecular Weight:

The USP 28 describes carboxy methyl cellulose sodium as the sodium salt of poly carboxy methyl ether of cellulose. Typical molecular weight is 90 000–700 000.

Structural Formula:



Functional Category

Coating agent, stabilizing agent, suspending agent, tablet and capsule disintegrant, tablet binder, viscosity-increasing agent, water-absorbing agent.

S No	Uses of Carboxy Methyl Cellulose Sodium.	Use Concentration (%)
1	Emulsifying agent	0.25- 1.0
2	Gel-forming agent	3.0- 6.0
3	Injections	0.05 – 0.75
4	Oral solutions	0.1 – 1.0
5	Tablet binder	1.0 – 6.0

Description:

Carboxymethylcellulose sodium occurs as a white to almost white, odorless, granular powder.

Moisture Content: `

Typically contains less than 10% water. However, carboxymethylcellulose sodium is hygroscopic and absorbs significant amounts of water at temperatures up to 378C at relative humidities of about 80%.

Solubility:

Practically insoluble in acetone, ethanol (95%), ether, and toluene. Easily dispersed in water at all temperatures, forming clear, colloidal solutions. The aqueous solubility varies with the degree of substitution (DS). various grades of Carboxy Methyl Cellulose Sodium are commercially available that have differing aqueous

Viscosities;

Aqueous 1% w/v solutions with viscosities of 5–13 000 mPa s (5–13 000 cP) may be obtained.

Applications in Pharmaceutical Formulation or Technology

- Carboxymethylcellulose sodium is widely used in oral and topical pharmaceutical formulations, primarily for its viscosityincreasing properties.
- Carboxymethylcellulose sodium may also be used as a tablet binder and disintegrant,(3–6) and to stabilize emulsions. Higher concentrations, usually 3–6%, of the medium viscosity grade are used to produce gels that can be used as the base for applications and pastes;

CROSPOVIDONE

Nonproprietary Names:

BP: Crospovidon, PhEur: Crospovidonum**,** USPNF: Crospovidone

Synonyms

Crosslinked povidone, E1202, Kollidon CL, Kollidon CL-M, Polyplasdone XL, Polyplasdone XL-10, poly vinyl poly pyrrolidone, PVPP, 1-vinyl-2-pyrrolidinone homopolymer.

Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Empirical Formula and Molecular Weight : (C6H9NO)n >1 000 000

Functional Category : Tablet disintegrant.

Description

Crospovidone is a white to creamy-white, finely divided, freeflowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Specific Surface Areas for commercial grades of Crospovidone

S no	Commercial grade	Surface area (m2/g)
1	Kollidon CL	1.0
2	Kollidon CL-M	3.0- 6.0
3	Polyplasdone XL	0.6 – 0.8
4	Polyplasdone XL	1.2 – 1.4

Applications in Pharmaceutical Formulation

- Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels.
- Larger particles provide a faster disintegration than smaller particles.
- Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs.

CROSCARMELLOSE SODIUM [46]

Nonproprietary Names

BP: Croscarmellose sodium, PhEur: Carmellosum natricum conexum

USPNF: Croscarmellose sodium

Synonyms

Ac-Di-Sol; crosslinked carboxymethylcellulose sodium, Explocel, modified cellulose gum, Nymcel ZSX, Pharmacel XL, Primellose, Solutab, Vivasol.

Chemical Name and CAS: Cellulose, carboxymethyl ether, sodium salt, crosslinked [74811-65-7]

Empirical Formula and Molecular Weight

Croscarmellose sodium is a Crosslinked polymer of carboxy Methyl Cellulose sodium.

Functional Category: Tablet and capsule disintegrant.

Description

Croscarmellose sodium occurs as an odorless, white or grayishwhite Powder

Particle size Distribution

Ac-Di-Sol: Not more than 2% retained on a #200 (73.7 mm) mesh and not more than 10% retained on a #325 (44.5 mm) mesh.

Pharmacel XL: More than 90% less than 45 mm, and more than 98% less than 100 mm in size.

Solubility: Insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

Applications

- Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules tablets, and granules.
- When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized.

- Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Uses of Croscarmellose Sodium

S no	Use	Concentration (%)
1	Disintegrant in capsules	10–25
2	Disintegrant in tablets	0.5–5.0

SODIUM STARCH GLYCOLLATE[46]

Nonproprietary Names

BP: Sodium starch glycollate, PhEur:Carboxymethylamylum natricum

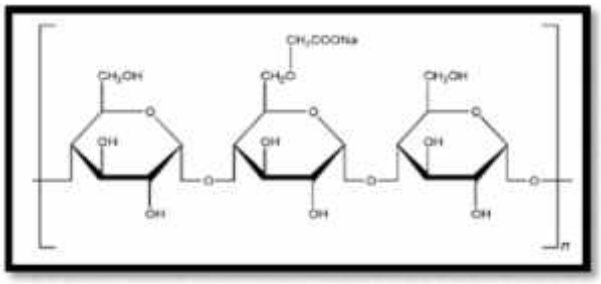
USPNF: Sodium starch glycolate

Synonyms

Carboxymethyl starch, sodium salt; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.

Chemical Name and CAS Number: Sodium carboxymethyl starch [9063-38-1]

Structural Formula:



Functional Category: Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation:

- Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations It is commonly used in tablets prepared by either direct compression or wet-granulation processes.

- Usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient.
- Disintegration occurs by rapid uptake of water followed by rapid and enormous Swelling Although the effectiveness of many disintegrants is affectedby the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired.

Description

Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. The PhEur 2005 states that it consists of oval or spherical granules, 30–100 mm in diameter, with some less-spherical granules ranging from 10–35 mm in diameter.

Particle size distribution: 100% of particles less than 106 mm in size. Average particle size is 35–55 mm for Explotab.

Solubility: sparingly soluble in ethanol (95%); practically insoluble in water. At a concentration of 2% w/v sodium starch glycolate disperses in cold water and settles in the form of a highly hydrated layer.

Swelling capacity: In water, sodium starch glycolate swells to up to 300 times its volume.

PRE GELATINISED STARCH[46]

Non-proprietary Name

BP: Pregelatinised starch, PhEur: Amylum pregelificatum

USPNF: Pregelatinized starch

Synonyms: Compressible starch, Instastarch, Lycatab C, Lycatab PGS, Merigel, National 78-1551, Pharma-Gel, Prejel, Sepistab ST 200, Spress B820, Starch 1500 G; Tablitz, Unipure LD, Unipure WG220.

Chemical Name and CAS Number: Pregelatinized starch [9005-25-8]

Empirical Formula and Molecular Weight: (C6H10O5)n where n = 300–1000

Functional Category: Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

Applications in Pharmaceutical Formulation

- Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent,(1,2) and disintegrant.
- In comparison to starch, grades of pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry-compression or direct compression processes.

Uses of Pre gelatinized Starch

S no	Use	Use concentration (%)
1	Diluent (hard gelatin capsules)	5–75
2	Tablet binder (direct compression)	5–20
3	Tablet binder (wet granulation)	5–10
4	Tablet disintegrant	5–10

Description

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste

Moisture content: pregelatinized maize starch is hygroscopic.

Particle size distribution: 30–150 mm, median diameter 52 mm. For partially pregelatinized starch, greater than 90% through a US #100 mesh (149 mm); and less than 0.5% retained on a US #40 mesh (420 mm).

Solubility: practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization. Pastes can be prepared

by sifting the pregelatinized starch into stirred, cold water. Cold-watersoluble matter for partially pregelatinized starch is 10–20%.

Viscosity (dynamic): 8–10 mPa s (8–10 cP) for a 2% w/v aqueous dispersion at258C.

SODIUM BICARBONATE[46]

Non-proprietary names: BP/EP: sodium bicarbonate

Synonym: Baking soda, e-500, and monosodium carbonate.

Chemical name: carbonic acid, monosodium salt, monosodium carbonate.

Empirical formula: NaHCO3

Molecular weight: 84.01

Category: alkalizing agent, therapeutic agent.

Description: it is an odorless, white crystalline powder with slight alkaline taste.

Acidity/ alkalinity: pH 8.3 for freshly prepared 0.1m aqueous solution at 250c.

Density: 2.159 g/cm3

Solubility: Soluble in water, practically insoluble in ethanol.

Stability and storage: Sodium bicarbonate is stable in dry air but slowly decomposes in Moist air and should therefore be stored in well-closed container in a cool dry place.

Safety: Orally ingested sodium bicarbonate neutralizes gastric acid with the evolution of carbon dioxide and may cause stomach cramps and flatulence.

Applications:

1. Employed as a source of carbon dioxide in effervescent tablets and granules.
2. Also used to buffer the drug molecules that are weak acids.
3. Used in solutions as buffering agent.
4. Also used as freeze-drying stabilizer.
5. As a gas forming agent.

MAGNESIUM STEARATE [46]

Nonproprietary names: BP- Magnesium stearate **Ph Eur**-Magnesia stearate
USP NF- magnesium stearate.

Synonyms: Stearic acid magnesium salt, Magnesium octadecanoate

Chemical name: Octdecanoic acid magnesium salt

Description: Magnesium stearate is a fine, white, precipitated, milled, impalpable powder of low bulk density, having a faint, characteristic odor and taste. The powder is greasy to touch and readily adheres to skin.

Applications:

1. Magnesium stearate is widely used in cosmetics, foods and pharmaceuticals.
2. It is primarily used as lubricant in capsule and tablet manufacture at a concentration between 0.25-5.0 % concentrations.
3. As an excipient, it is mainly used as directly compressible tablet diluents.
4. Also used in micro sphere formulations
5. Used to absorb liquids, such as flavours in tabletting process.

MICRO CRYSTALLINE CELLULOSE [46]

Nonproprietary Names

BP: Microcrystalline cellulose, JP: Microcrystalline cellulose,
PhEur: Cellulosum microcristallinu, USPNF: Microcrystalline cellulose

Synonyms

Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

Chemical Name and CAS Registry Number: Cellulose [9004-34-6]

Empirical Formula and Molecular Weight: (C6H10O5)n _36 000 where n _ 220.

Functional Category: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Uses :

S no	Use	Concentration (%)
1	Adsorbent	20–90
2	Antiadherent	5-20
3	Capsule binder/diluent	20-90
4	Tablet disintegrant	1-15
5	Tablet binder/diluent	20-90

Melting point: Chars at 260–2708C.

Moisture content: Typically less than 5% w/w. However,different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.

Solubility: slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Applications in Pharmaceutical Formulation

- Primarily as a binder/diluent in oral tablet and capsule Formulations where it is used in both wet-granulation and Direct-compression processes. in addition to its use as a Binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in Tableting.
- Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

LACTOSE ANHYDROUS [46]

Nonproprietary Names: BP: Anhydrous lactose**,** JP: Anhydrous lactose

PhEur: Lactosum anhydricum, USPNF: Anhydrous lactose

Synonyms

Anhydrous Lactose NF 60M, Anhydrous Lactose NF Direct Tableting, Lactopress Anhydrous, lactosum, lattioso, milk sugar, Pharmatose DCL 21, Pharmatose DCL, saccharum lactis, Super-Tab Anhydrous.

Chemical Name: O-b-D-galactopyranosyl-(1!4)-b-D-glucopyranose

Empirical Formula and Molecular Weight: C12H22O11 342.30

Functional Category: Binding agent; directly compressible tableting excipient; lyophilization aid; tablet and capsule filler.

Applications in Pharmaceutical Formulation

Anhydrous lactose is widely used in direct compression tableting applications and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content.

Description

Lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous b-lactose and anhydrous a-lactose. Anhydrous lactose typically contains 70–80% anhydrous b-lactose and 20–30% anhydrous a-lactose.

Melting point

223.08C for anhydrous a-lactose;
252.28C for anhydrous b-lactose;
232.08C (typical) for commercial anhydrous

Solubility: Soluble in water; sparingly soluble in ethanol (95%) And ether.

Specific Surface Area: 0.41m2/g for Pharmatose DCL 22; 0.37m2/g for Super-Tab Anhydrous.

POLY VINYL PYROLLIDINE [46]

Nonproprietary Names:

BP: Povidone, JP: Povidone, PhEur: Povidonum, USP: Povidone

Synonym

E1201, Kollidon, Plasdone, poly[1-(2-oxo-1-pyrrolidinyl)ethylene], polyvidone, polyvinylpyrrolidone, PVP, 1-vinyl-2-pyrrolidinone polymer.

Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Empirical Formula and Molecular Weight: (C6H9NO)n 2500–3 000 000

Approximate Molecular Weights for different grades of Povidone

K-value Approximate molecular weight

Functional Category: Disintegrant; dissolution aid; suspending agent; tablet binder.

Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

Melting point: softens at 1508C.

Moisture content: povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities.

Solubility: Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Applications in Pharmaceutical Formulation

- Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet granulation processes.
- Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage for forms. Povidone solutions may also be used as coating agents

Uses of Povidone

S no	Use	Use concentration
1	Carrier for drugs	10-25
2	Dispersing agent	Up to 5
3	Eye drops	2-10
4	Suspending agent	Up to 5
5	Tablet binder, tablet diluent, or coating agent	0.5-5

5. PLAN OF WORK

The present study was carried by formulating and developing bi layer tablets of Metformin Hcl Floating SR layer and Sitagliptin IR layer and evaluating them for in vitro drug release profiles, post compression parameters and mechanism of drug release.

The plan of the work in brief consists of the following steps :

Step – 1 Preformulation studies of **Metformin Hcl** And **Sitagliptin Phosphate** drug substances.

- Description
- Melting point
- Solubility
- IR spectrum
- Determination of λ maximum by UV spectrum.
- Assay
- Drug excipient compatibility study

Step – 2 Construction of calibration curves for both Metformin Hcl And Sitagliptin Phosphate by UV spectrophotometer.

Step – 3 Formulation of Metformin Hcl floating SR layer tablets by using HPMC Sodium CMC.

Step – 4 Formulation of Sitagliptin IR layer by using Superdisintegrants.

Step – 5 Evaluation of Precompression Parameters of Metformin Granules and Sitagliptin Blend.

Step – 6 Evaluation of Floating Behaviour, Swelling Study for Metformin tablets.

Step - 7 Disintegration test and Evaluation of Post compression parameters for both tablets.

Step – 8 In vitro dissolution study of Metformin SR tablets andselecting the best formulation from the results.

Step – 9 In vitro dissolution study of sitagliptin IR tablets and selecting the best formulation from the results.

Step – 10 Compression of the Bi layer tablet having with best formulations of Metformin SR and Sitagliptin IR tablets respectively.

Step – 11 Evaluation of the bi layer tablets

- Post compression parameters of the bilayer tablets.
- Floating (or) In vitro buoyancy test.
- In vitro Disintegration test for Sitagliptin layer.
- In vitro dissolution study of the bilayer tablets for the release of Sitagliptin and Metformin Hcl.
- Swelling study.

Step – 12 Comparision of in vitro drug release profiles of both drugs with respective marketed formulations.

Step - 13 Kinetic studies (or) fitting of in vitro drug release data into various model.

Step – 14 Stability Studies of bilayer tablets as per ICH guidelines.

6. MATERIALS AND METHODS

6.1. A MATERIALS USED

Table – 01: **List of Drugs and Excipients used in the study.**

S.No	Materials	Manufacturers / Suppliers
1	Metformin hydrochloride	Micro labs
2	Sitagliptin phosphate	Micro labs
3	HPMC K 100M (Methocel)	Vivimedpharma, Hyderabad
4	Sodium CMC	Vivimedpharma, Hyderabad
5	PVP K30	Vivimedpharma, Hyderabad
6	Lactose	Vivimedpharma, Hyderabad
7	Microcrystalline cellulose (Avicel)	Vivimedpharma, Hyderabad
8	Sodium bicarbonate	S.D Fine Chemicals, Mumbai
9	Magnesium stearate	S.D Fine Chemicals, Mumbai
10	Iso propyl alcohol	S.D Fine Chemicals, Mumbai
11	Pregelatinised starch	S.D Fine Chemicals, Mumbai
12	Cross povidone	S.D Fine Chemicals, Mumbai
13	Cross carmellose sodium	Vivimedpharma, Hyderabad
14	Sodium starch glycollate	Vivimedpharma, Hyderabad
15	Iron oxide – Red	Vivimedpharma, Hyderabad

6.1.B INSTRUMENTS USED

Table - 02: List of Equipments used in the study

S no	Equipment / Instruments	Manufacturer
1	Electronic Weighing Balance	Mettler
2	Sieve no # 40 and # 28	Jaico metals
3	Hot air oven	Thermo lab
4	Tablet punching machine	CJD3-3 Cadmach
5	Tablet Hardness Tester	Inlap
6	Friability Tester	USP (EF-2), Electro lab
7	Vernier caliper	ICI
8	Dissolution Tester (USP type II)	Lab India
9	Disintegration Tester	USP Lab india
10	Melting Point Apparatus	Systronic
11	UV-VIS. Spectrophotometer	Lab india
12	Stability control oven(40ºC/75 RH)	Thermo lab
13	pH Meter	Systronic
14	FT-IR Spectrophotometer	Spectrum RXI-FTIR Perkin Elimer

6.2 METHODOLOGY

6.2.1 PREFORMULATION STUDIES

Preformulation may be described as a phase of the dosage form development process which consists of characterization of the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe & effective dosage forms.

Here preformulation studies were conducted for both drugs **Metformin Hydrochloride** and **Sitagliptin Phosphate.**

A) Identification and characterization of the drug

i . Description

The drug samples obtained were examined for their state, appearance, colour**,** odour etc.

ii . Melting point

The melting point of the drug substances was determined by using melting point apparatus (PMP-D, Veego). The melting point was determined by introducing small amount of substance in the capillary attached to graduated thermometer and constant heat was applied with the assembly suspended in the paraffin bath. The drug samples were tested in temperature range of 100-250^{0}C and point at which drug melts was noted. The melting points were reported in sections - 7.11 & 7.12.

iii . Solubility

Solubility of the Metformin Hydrochloride And Sitagliptin Phosphate were determined in different solvents like water, 0.1 N Hcl, phosphate buffer pH 6.8, alcohol, acetone etc.

IV. IR absorption spectrum

FT-IR spectra of drug samples were recorded using potassium bromide (KBr) pellet method at resolution of 4cm^{-1} for its authentication and to study principle peaks using FT-IR spectrophotometer (FT-IR 8400S, Shimadzu). Dry sample of drug and potassium

bromide was mixed uniformly and filled into the die cavity of sample holder and an IR spectrum was recorded. The identified peaks were compared with the principle peaks of reported IR spectrum. Thus the samples were authenticated. The FT-IR spectra of Metformin HCl and Sitagliptin phosphate were shown in Figures -7.1 & 7.8.

V. UV spectra

- UV- Spectrum of pure Metformin HCl was observed in 0.1 N Hcl (pH 1.2) as a medium. Drug (10 mg) was dissolved in 100 ml 0.1 N Hcl to obtain the stock solution of concentration 100 µg/mL. From this stock solution, 1mL was withdrawn and diluted upto 10 mL and resultant solution was scanned between 200-400 nm to determine its absorption maxima using UV- spectrophotometer (labindia). It should give peak corresponding to its λmax at 233 nm. The UV spectrum of Metformin HCl is shown in Fig – 7.2.
- UV- Spectrum of pure Sitagliptin Phosphate was taken in 0.1 N Hcl (pH 1.2) as a medium. Drug (10 mg) was dissolved in 100 ml 0.1 N Hcl to obtain the stock solution of concentration 100 µg/mL. From this stock solution, 1mL was withdrawn and diluted upto 10 mL. and resultant solution was scanned between 200-400 nm using UV- spectrophotometer. It should give peak corresponding to its λmax at 267 nm. The UV spectrum of Sitagliptin Phosphate is shown in fig –7.9.

V. Assay

Metformin Hcl

- The assay procedure for authentification of Metformin HCl was carried out as per Procedure reported in USP 30 NF 25 2007.

  Procedure: Weigh accurately about 60 mg of Metformin HCl, dissolve in 4 ml of anhydrous formic acid, add 50 ml of acetic anhydride and carry out non-aqueous titration, determining the end-point potentiometrically. Perform a blank determination and make any necessary correction.

Each ml of 0.1 N Perchloric acid is equivalent to 0.008281 g of $C_4H_{11}N_5$, HCl.

Sitagliptin Phosphate

Procedure: Different aliquots of working standard solutions containing 2-10 µg of STP was transferred into a series of serially numbered 10ml volumetric flasks. The flasks were diluted to 10 ml with distilled water. The absorbance of the solution was measured at 267 nm using water as a blank. The amount of sitagliptin phosphate present in the sample was computed from the corresponding calibration curve.

6.2.2 PREPARATION OF CALIBRATION CURVE

A) Metformin Hcl

Preparation of 0.1 N Hcl: 85 ml of Hydrochloric Acid was taken and diluted with water to 1000 ml to obtaine 0.1 N Hydrochloric Acid.

Procedure:

10 mg of pure Metformin Hcl was accurately weighed and transferred to 100 ml volumetric flask. The drug was initially dissolved in 50 ml of 0.1 N Hcl Solution with shaking and the volume was made up to the mark with the same solvent to obtain standard stock solution A of concentration 100 µg/ ml. From the above stock solution A 1 ml was withdrawn and transferred to 10 ml volumetric flask and was diluted up to the mark with 0.1 N Hcl to obtain secondary stock B of concentration 10 µg/ ml.

Appropriate dilutions of the secondary standard stock solution B was done by withdrawing 1,2,3,4,5 ml of samples from B and diluting with 0.1 N Hcl to get the concentrations of 1,2,3,4,5 µg/ ml. The absorbance of these working standard solutions were obtained in the quantitative mode of the instrument at 233 nm which is the λ max of Metformin Hcl. The absorbance of different concentration of Metformin Hcl are reported Table no -7.2 and the calibration curve is shown in Fig -7.3 .

B) **Sitagliptin Phosphate**

Preparation of 0.1 N Hcl: : 85 ml of Hydrochloric Acid was taken and diluted with water to 1000 ml to obtain 0.1 N Hydrochloric Acid.

Procedure : 10 mg of pure Sitagliptin Phosphate was accurately weighed and transferred to 100 ml volumetric flask. The drug was initially dissolved in 50 ml of 0.1 N Hcl with shaking and the volume was made up to the mark with the same solvent to obtain standard stock solution A of concentration 100 µg/ ml. From the above stock solution A 1,2,3,4,5,6,7….10 m samples were withdrawn and transferred to 10 ml volumetric flasks and were diluted up to the mark with 0.1 N Hcl to obtain secondary stock solutions having concentration 10,20,30,40,50,60,70…100 µg/ ml respectively.

The absorbance of these samples were measured at 267 nm which is the λ max of Sitagliptin Phosphate . The absorbance of different concentration of Sitagliptin phosphate were reported in Table no -7.3 and the calibration curve is shown in Fig – 7.10.

6.2.3 DRUG – EXCIPIENT COMPATIBILITY

The selected drug and polymers were characterized by FT-IR spectroscopy and the FTIR spectra of the pure drug **Metformin Hcl** with used excipients like HPMC K100M, sodium CMC, Microcrystalline cellulose, PVP K30, magnesium stearate etc. and **Sitagliptin Phosphate** with excipients like crospovidone , croscarmellose sodium, sodium starch glycolate and pre gelatinised starch were recorded to know the drug-excipient interactions.

The instrument was operated under dry air purge and the scans were collected at scanning speed 2 mm/sec with resolution of 4 cm^{-1} over the region 4000-400 cm^{-1}. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction. The FT-IR spectra of pure Metformin Hcl, Sitagliptin Phosphate and the spectra of drug excipient mixtures were shown in fig – 7.4 -7.7 and 7.11 – 7.15 respectively.

6.2.4 FORMULATION AND DEVELOPMENT

The proposed bi - layer tablet contains two layers. They are

1. Floating sustained release layer containing Metformin Hydrochloride.
2. An immediate release layer containing Sitagliptin.

6.2.4.1 FORMULATION OF METFORMIN HCL LAYER

Different formulations of sustained release floating tablets of Metformin Hcl layer (F1-F10) were prepared by **wet granulation** method by using different excipients Like HPMC K100 M, Sodium CMC as release retarding polymer, PVP K 30 as a binder, Sodium Bicarbonate as an effervescent agent, Magnesium Stearate as a lubricant..

The dose of Metformin Hcl for sustained release was taken as 500 mg based on the dose calculation.

Dose Calculation

Total dose of Metformin for sustained release formulation was calculated by the following equation using available pharmacokinetic data.

$$\mathbf{Dt= D(1 + 0.639\ X\ t/t_{1/2})}$$

Where, Dt=Total dose of Drug, D = Dose of immediate release part (250 mg), t= time(hours) during which the sustained release is desired (12hours), $t_{1/2}$= half-life of the drug (6.2Hours).

Here, for Metformin Hcl 250 mg is the conventional dose. Therefore, dose of metformin equivalent to 250 mg of Metformin Hcl is 213.5 mg.

$$Dt = 213.5(1+0.639X12/6.2)= 477.55 \text{ mg.}$$

Hence, the dose of Metformin for sustained release tablet was taken as 500 mg.

Procedure for wet granulation:

Step 1 – **Sifting**:

Appropriate quantities of Metformin HCl, and excipients like HPMC K100 M, Sodium CMC, PVP K 30 and Sodium Bicarbonate were measured accurately and all the measured powders were sifted through Seive no # 40.

Step 2 – **Dry Mixing:**

The above sifted materials were mixed rapidly for 5 min and again passed through sieve no 40.

Step 3 – Granulation:

Iso Propyl Alcohol having 2% w/v amount of PVP K- 30 was used as the granulating solution and the solution was added to the mixture in step 2 and was kneaded for 2-5 min, then the kneaded mass was passed through sieve no # 20 to obtain the granules.

Step 4 – **Drying Of Granules:**

The granules obtained in step 3 were dried in a tray drier at 50°C for 2 hrs.

Step 5 – Lubrication:

The dried granules were lubricated uniformly with weighed quantities of magnesium stearate.

Step 6 – Compression:

The above granules were compressed into tablets by CADMACH multi station tablet compression machine by using 9 mm punch.

In Batch F1 to F3, HPMC K100M was used as the sustained release polymer and in Batch F4 & F5 sodium CMC was used and in F6 – F8 combination of HPMC K100M and sodium CMC was used as Polymer and in Batch F9 & F10 only HPMC K100M was used as the release retarding polymer

TABLE – 6.3: Formulations Of The Metformin Hcl Floating Sustained Release Layer

S no	**INGREDIENTS (mg)**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
1	Metformin Hcl	500	500	500	500	500	500	500	500	500	500
2	HPMC K 100M	100	125	150	-	-	100	100	100	150	150
3	Sodium CMC	-	-	-	100	150	25	50	75	-	-
6	PVP K30	30	30	30	30	30	30	30	30	30	30
7	Sodium Bicarbonate	10	10	10	10	10	10	10	10	25	50
8	Magnesium Stearate	5	5	5	5	5	5	5	5	5	5
9	Iso Propyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
10	Total Weight	645	670	695	645	695	670	695	720	710	735

6.2.4.2 FORMULATION OF SITAGLIPTIN IMMEDIATE RELEASE LAYER

Different formulations of sitagliptin IR tablets containing the drug with excipients like pre gelatinised starch, microcrystalline cellulose, cross povidone, croscarmellose sodium, sodium starch glycolate, poly vinyl pyrollidine, magnesium stearate were prepared by **Direct Compression** method.

Procedure:

Step 01 – Sifting:

Sitagliptin and other excipients like pre gelatinised starch, microcrystalline cellulose, cross povidone, croscarmellose sodium, sodium starch glycolate, poly vinyl pyrollidine were sifted through sieve no 40 #.

Step 02 – Blending:

The sifted powders were thoroughly mixed for approximately 5 min and again passed through sieve no 40 # for maintaining uniformity in particle size.

Step 03 – Lubricating:

Above mixture was lubricated for 2 min with Magnesium Stearate which was already passed through sieve 60.

Step 04 – colouring:

The colour iron oxide red (0.125% w/w) was passed through the sieve number # 100 and added to the above mixture and blended uniformly to ensure uniform colour.

Step 05 – compression:

Then the tablets were compressed by using CADMACH multistation compression machine with 6mm bi concave punches.

For Batches F1 to F3 crospovidone, F4 to F6 croscarmellose sodium and in F7 to F9 sodium starch glycolate were used as superdidintegrants.

Table – 04: Formulations Containing Sitagliptin Immediate Release Layer (in mgs)

S no	INDREDIENTS (mg)	S1	S2	S3	S4	S5	S6	S7	S8	S9
1	Sitagliptin	50	50	50	50	50	50	50	50	50
2	Pre gelatinised Starch	100	100	100	-	-	-	-	-	-
3	Microcrystalline Cellulose	80	75	72.5	100	100	100	30	150	87.5
4	Lactose	-	-	-	80	75	72.5	150	27.5	87.5
5	Crospovidone	5	10	12.5	-	-	-	-	-	-
6	Croscarmellose Sodium	-	-	-	5	10	12.5	-	-	-
7	Sodium Starch Glycolate							5	7.5	10
8	PVP K30	10	10	10	10	10	10	10	10	10
9	Magnesium Stearate	5	5	5	5	5	5	5	5	5
10	Iron Oxide Red	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
11	Total	250	250	250	250	250	250	250	250	250

6.2.4.3 EVALUATION OF PRE COMPRESSION PARAMETERS OF BOTH TABLETS

Several Pre compression parameters of Metformin Hcl granules and Sitagliptin blend were evaluated as follows:

a) Angle of Repose

Angle of repose has been defined as the maximum angle possible between the tangent to the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method. The granules mass was allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of granules on the paper. The angle of repose was calculated

by substituting the values of the base radius 'R' and pile height 'H' in the following equation.

$$\tan \theta = H / R$$

$$\text{Therefore, } \theta = \tan^{-1} (H / R)$$

$$\tan \theta = h/r$$

$$\text{Hence, } \theta = \tan^{-1} h/r$$

Where, θ = angle of repose

h = height of the cone

r = radius of the cone base

Table – 05 Relationship between angle of repose (θ) and flowability

Angle of Repose (θ)	FLOWABILITY
< 20	Excellent
20 – 30	Good
30 – 34	Passable
> 40	Very poor

b) Bulk Density

The bulk density was obtained by dividing the mass of a powder by the bulk volume in cm^3. It was calculated by using equation given below:

$$\rho_b = M / V_0$$

Where, ρ_b = bulk density

M = weight of sample in grams

V_0 = Apparent unstirred volume

c) Tapped Density

The tapped density was obtained by dividing the mass of a powder by the tapped volume in cm^3. It was calculated by using equation given below:

$$\rho_t = M / V_f$$

Where, ρ_t = Tap density

M = weight of sample in grams

V_f = final Tap volume

d) Carr's Index: The Carr's index is also called as the compressibility index. The Carr's index is determined from the tapped density and poured density (bulk density) as per the formula given below.

$$\text{Carr's index (\%)} = \frac{\text{Tapped density- bulk density}}{\text{Tapped density}} \times 100$$

Table – 06 Relationship between % Compressibility and Flowability

% Compressibility	Flowability
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
23 – 35	Poor
33 – 38	Very Poor
> 40	Extremely Poor

e) Hausner ratio: Hausner ratio is determined from the ratio of tapped density to poured density using formula given below.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Poured density}}$$

Table no - 07 Hausner's Ratio Limits

Flow character	Hausner's Ratio
Excellent	1.00-1.11
Good	1.12-1.18
Fair	1.19-1.25
Passable	1.26-1.34
Poor	1.34-1.45
Very poor	1.46-1.59
Very, very poor	>1.60

The Angle of repose, Bulk density, Tap density, Carr's index and Hausner ratio of both the formulations were reported in sec -7.2

6.2.5 EVALUATION OF THE COMPRESSED TABLETS

6.2.5.1 In vitro buoyancy study of Metformin Hcl floating tablets

In vitro buoyancy studies were performed to determine the floating lag time and total floating time of the tablets. They are performed as per the method described by Rosa et al. The tablets were placed in 100 ml beaker containing 0.1N hydrochloric acid of pH 1.2 at temperature of 37 °C.

Floating lag time: The time required for the tablet to rise to the surface of the beaker and float was determined as the floating lag time.

Total floating time

The total time duration for which the tablet constantly remained on the surface of the medium was determined as the total floating time.

Tablet density

Tablet density is an important parameter for the floating tablets. The tablet will float when its density is less than that of the gastric fluids (1.004g/cc). when tablet comes in contact with the gastric fluid it will float by releasing the co_2 gas (because of the effervescent agent sodium bi carbonate) as its density is less than gastric fluids.

The density of the tablet was determined as follows :

$$D = m/v$$

D = density

M = mass or weight of the tablet

V = volume of the tablet (cc) ($v = \pi r^2 h$)

6.2.5.2 Swelling Study of Metformin Hcl Tablets

The swelling behaviour of a dosage form is measured by studying its weight gain or water uptake. Water uptake is measured in terms of percent weight gain, as given by the equation. The individual tablets were kept in 50 ml of water. Tablets were taken out after every 1 hr up to 5 hrs, blotted with filter paper to remove water on the surface and weighed accurately. The % swelling (or) water uptake (%WU) was measured as:

$$\%WU = \frac{WT - W0}{W0} X\ 100$$

Wt = Weight of dosage form at time t.

W0 = Initial weight of dosage form.

6.2.5.3 In-vitro Disintegration test for Sitagliptin Tablets

The in-vitro disintegration test was performed to determine the disintegration time. A tablet was placed in each of the six tubes of the apparatus and one disc was placed on each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured.

6.2.5.4 Evaluation of Post Compression Parameters

The compressed **Metformin Hcl** SR tablets and **Sitagliptin** IR tablets were evaluated for the post compression parameters like Hardness, Friability, Weight Variation, Thickness, Drug Content Uniformity etc.

a) Shape of Tablets:

Tablets were examined under the magnifying lens for the shape of the tablet.

b) Tablet Dimensions:

Thickness and diameter were measured using a calibrated vernier caliper. Tablets of

each formulation were picked randomly and thickness was measured individually.

c) **Hardness:** Hardness is the ability of the tablet to withstand the mechanical shocks under conditions of storage, transportation and handling before usage by a patient and it depends on the strength of tablet. The hardness of tablet of each formulation was measured by Pfizer hardness tester. The hardness was measured in terms of kg/cm^2. For each batch three tablets were picked randomly and tested for hardness tested.

d) Friability

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure.

Procedure: Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min (or) 100 revolutions, the tablets were weighed and the % friability was calculated measured using the formula.

$$\% \text{ Friability} = \frac{\text{Initial weight of tablets- Final weight of tablets}}{\text{Initial weight of tablets}} \times 100$$

Limits: Percentage friability of tablets less than 1% is considered acceptable.

e) Weight variation test

USP procedure for weight variation test was followed which is as follows:

Twenty tablets were randomly selected from each batch and individually weighed by using Electronic balance (Shimatzu). The average weight and standard deviation of twenty tablets were calculated. Not more than two of the individual weights should deviate from the average weight by more than the % deviation mentioned in the table

Table – 06 Limits for weight variation

S no	Average weight of tablet (X mg)	Percentage deviation allowed
1 2 3	130 mg or less 130-324 mg More than 324 mg	10 7.5 5

% Maximum positive deviation **= (W_H – A/A)** ×100

% Minimum negative deviation = (A – W_L/ A) × 100

Where

W_H = highest weight in mg.

W_L = lowest weight in mg.

A = average weight of tablet in mg.

f) **Drug Content Uniformity**

Metformin Hcl

The Drug content uniformity of Metformin HCl was carried out as per Procedure reported in I.P 1996.

Procedure:

From each formulation 5 tablets were seleted randomly, crushed and powdered. The powder equivalent to 60 mg of Metformin Hcl was weighed and dissolved in 4 ml of anhydrous formic acid, 50 ml of acetic anhydride was added and non-aqueous titration was carried out, determining the end-point potentiometrically. A blank determination was made and necessary correction was made.

Each ml of 0.1 M perchloric acid is equivalent to 0.008281 g of $C_4H_{11}N_5$, HCl

Sitagliptin Phosphate

Standard preparation

10 mg of sitagliptin was weighed and dissolved in 100 ml water to obtain the stock solution of concentration 100 µg/mL. From this stock solution, 1mL was withdrawn and diluted up to 10 mL with water to obtain the concentration of 10 µg/ml.

Sample preparation:

From each formulation 5 tablets were combined and thoroughly crushed. An amount of tablet powder equivalent to average weight of one tablet (100mg) was accurately weighed and transferred to a 100 ml volumetric flask, to this 30 ml double distilled water was added. The content of the flask was sonicated for 15 min and the volume was made up to mark with water. The solution was filtered filter through Whatmann filter paper No. 40. Appropriate solutions were prepared by taking suitable aliquots and diluting them with double distilled water to give final concentration (10 µg/ml). Then the absorbance of these solutions was measured at 267 nm.

Percentage drug content was calculated as follows:

$$\% \text{ drug content} = \frac{At\ Cs\ P}{As\ Ct} \times \frac{100}{100}$$

At = absorbance of test sample

As = absorbance of the standard preparation

Ct = concentration of the test sample

Cs = concentration of the standard preparation

P = standard potency (99.7)

6.2.5.5 IN VITRO DISSOLUTION STUDY

A) Metformin Hcl Floating SR Tablets

In vitro dissolution study was performed using USP Dissolution Testing Apparatus II (Electrolab). The dissolution test was performed using 900 ml of 0.1 N HCL, at 37 ± 0.5^0C with paddle agitation at 100 rpm. 10 ml samples were withdrawn from the dissolution vessels at the time intervals of 1, 2, 4, 6, 8, 10,12hrs and the samples were replaced with fresh dissolution medium equilibrated at the same temperature to maintain the volume. The samples were filtered through Whatman filter paper no. 41.The samples collected were diluted appropriately to attain the concentration of 10 µg/ml with the same medium. Samples were then analyzed by UV spectrophotometer at 233 nm. Then the % drug release was calculated from the absorbance values and is reported in sec 7.3.4.

Details of Dissolution Test

- Apparatus : USP Type – II (Paddle)
- Volume of medium : 900 ml
- Temperature : 37± 0.5 ^{o}C
- Paddle Speed : 100 rpm
- Dissolution medium used : 0.1 N HCL
- Aliquot taken at each time interval : 10 ml

B) **Sitagliptin Phosphate IR Tablets**

In vitro dissolution study was performed using USP Dissolution Testing Apparatus II (Electrolab). The dissolution test was performed using 900 ml of 0.1 N HCL, at 37 ± 0.5^0C with paddle agitation at 50 rpm. 10 ml samples were withdrawn from the dissolution vessels at the time intervals of 5, 10, 15, 20, 30, 40, 60 min and the samples were replaced with fresh dissolution medium equilibrated at the same temperature to maintain the volume. The samples were filtered through Whatman filter paper no. 41.The samples collected were diluted appropriately to attain the

concentration of 10 µg/ml with the same medium. Samples were then analyzed by UV spectrophotometer at 267 nm. Then the % drug release was calculated from the absorbance values and is reported in sec 7.4.3 .

Details of Dissolution Test:

- Apparatus : USP Type – II (Paddle)
- Volume of medium : 900 ml
- Temperature : 37± 0.5 ^{o}C
- Paddle Speed : 50 rpm
- Dissolution medium used : 0.1 N HCL
- Aliquot taken at each time interval : 10 ml

6.2.5.6 Selection of the Best Formulations

From the dissolution profiles of both the drugs best formulations were selected from Metformin Hcl floating SR tablets and Sitagliptin IR tablets formulations by comparing them with the marketed formulations.

GLUCOPHAGE XR (500MG) tablets and JANUVIA (50MG) tablets were used as the marketed samples for Metformin and Sitagliptin respectively.

6.2.6 PREPARATION OF BI LAYER TABLETS

Bi-layer tablets of Metformin and Sitagliptin were prepared by taking the best formulations from Metformin Hcl SR floating tablets and Sitagliptin IR tablets.

Granules of Metformin layer were first introduced into the die cavity, a slight compression was made and then Sitagliptin blend was introduced into the die cavity followed by final compression with optimum hardness to form the bi layer tablets. Here compression was made by using 16 station tablet compression machine (Cadmach, India) with 12 mm capsule shaped punches.

Only one batch of the bi layer tablets containing best formulations from both layers were prepared and evaluated for various physical properties and dissolution profile was compared with respective marketed formulations.

6.2.6.1 EVALUATION OF THE BILAYERED TABLETS

A) Post Compression Parameters of The Bi Layered Tablets

The prepared bi layer tablets of Metformin Hcl and Sitagliptin were evaluated for the following physic chemical properties

a) Shape of Tablets

Tablets were examined under the magnifying lens for the shape of the tablet.

b) Tablet Dimensions

Thickness and diameter were measured using a calibrated vernier callipers . Bi layer Tablets were picked randomly and thickness was measured individually.

c) **Hardness**

Hardness is the ability of the tablet to withstand the mechanical shocks under conditions of storage, transportation and handling before usage by a patient and it depends on the strength of tablet. The hardness of tablet of each formulation was measured by Pfizer hardness tester. The hardness was measured in terms of kg/cm^2. For each batch three tablets were picked randomly and tested for hardness tested.

d) Friability

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure.

Procedure: Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min (or) 100 revolutions, the tablets were weighed and the % friability was calculated measured using the formula.

$$\% \text{ Friability} = \frac{\text{Initial weight of tablets- Final weight of tablets}}{\text{Initial weight of tablets}} \times 100$$

Limits: Percentage friability of tablets less than 1% is considered acceptable.

e) Weight variation test

USP procedure for weight variation test was followed which is as follows:

Twenty tablets were randomly selected from each batch and individually weighed by using Electronic balance (Shimatzu). The average weight and standard deviation of twenty tablets were calculated. Not more than two of the individual weights should deviate from the average weight by more than the % deviation mentioned in the table

Table – 06 Allowable limits for weight variation

S no	Average weight of tablet (X mg)	Percentage deviation Allowed
1	130 mg or less	10
2	130-324 mg	7.5
3	More than 324 mg	5

% Maximum positive deviation **= (W_H – A/A)** ×100

% Minimum negative deviation = $(A - W_L / A) \times 100$

Where

W_H = highest weight in mg.

W_L = lowest weight in mg.

A = average weight of tablet in mg.

f) **Drug content of the Bilayer tablets**

Twenty tablets were accurately weighed and crushed to fine powder. Powder equivalent to 10 mg of Metformin HCl and 1mg of Sitagliptin was weighed and dissolved in distilled water, sonicated for 10 min and filtered through Whatman's filter paper no.41. After rejecting first few ml, different concentrations of tablet sample were

prepared by serial dilution technique and scanned over the range of 400-200 nm in multi-component mode and analyzed at 233 and 267 nm wavelength.

6.2.6.2 In-Vitro Dissolution Study Of The Bi Layered Tablet

In vitro dissolution study of the bi- layer tablet containing Metformin Hcl SR floating layer and Sitagliptin immediate release layer was performed as follows:

The dissolution was performed over a 12 hr period for bi layer tablets using USP type II (paddle) Dissolution Testing Apparatus (Electrolab). 900ml of 0.1N Hcl was used as dissolution medium agitated at 100 RPM, at temperature of 37± 0.5 ^{0} C. 10 ml samples were withdrawn at 5,10,15,20,30,40,60 min for 1 hr to estimate the release of Sitagliptin, and at 1, 2, 4, 6, 8, 10, 12 hrs for estimating Metformin release. Same volume of dissolution medium was replaced at every time interval, Samples were filtered by whatman filter paper no. 41. The samples were analyzed for Metformin Hcl and Sitagliptin by UV Spectrophotometry at their respective λ max values 233 nm and 267 nm.

The samples collected for first hour were analyzed for Sitagliptin content at 267 nm in UV spectrophotometer by keeping the solution containing Metformin Hcl formulation as blank to minimize the interference.

The samples collected for 1 – 12 hrs were analyzed for the release of Metformin Hcl at 233 nm in UV spectrophotometer by keeping the solution containing Sitagliptin formulation as blank to minimize the interference.

Conditions of Dissolution Test:

- Apparatus : USP Type – II (Paddle)
- Volume of medium : 900 ml
- Temperature : 37± 0.5 ^{o}C
- Paddle Speed : 100 rpm
- Dissolution medium used : 0.1 N Hcl (pH 1.2)
- Aliquot taken at each time interval : 10 ml

From the absorbance values obtained in above steps cumulative % drug release of both Metformin Hcl and Sitagliptin were calculated.

6.2.6.3 Comparative Study

From the prepared bi layer tablet the in vitro drug release profile of the two formulations i.e Metformin Hcl floating SR layer and Sitagliptin IR layer were compared with their respective marketed tablets.

6.2.7 Kinetic Studies for estimating the mechanism of drug release

The methods of approach to investigate the kinetics of drug release from controlled release formulation can be classified into three categories:

- **Statistical methods**: (Exploratory data analysis method, repeated measures design, multivariate approach).
- **Model dependent methods** : (Zero order, first order, Higuchi, Korsmeyer-Peppas model, Hixson Crowell, Baker-Lonsdale model**,** etc)
- **Model independent methods** : (Difference factor (f1), similarity factor (f2))

To analyze the mechanism of the drug release, the in vitro dissolution data obtained was fitted into the following models:

1) Zero-order model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q0\ n\ Qt = K0t \quad (1)$$

Rearrangement of equation (1) yields:

$$Qt = Q0 + K0t \quad (2)$$

Where: Qt is the amount of drug dissolved in time *t,*

Q0 is the initial amount of drug in the solution (most times, Q0 = 0) and

K0 is the zero order release constant expressed in units of concentration/time.

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as Cumulative amount of drug released *versus* time

2) First order model

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the equation:

$$dc/dt = - Kc \quad ---(3)$$

Where *K* is first order rate constant expressed in units of time-1.

Equation (3) can be expressed as:

$$\log C = \log C0 \text{ n } Kt / 2.303 \quad (4)$$

Where C0 is the initial concentration of drug,

k is the first order rate constant, and

t is the time .

The data obtained are plotted as log cumulative percentage of drug remaining *vs*. time which would yield a straight line with a slope of n K/2.303

3) Higuchi model:

The first mathematical model aimed to describe drug release from a matrix system was proposed by Huguchi in 1961 . This model is based on the hypotheses that (i) initial drug concentration in the matrix is much higher than drug solubility; (ii) drug diffusion takes place only in one dimension (edge effect must be negligible); (iii) drug particles are much smaller than system thickness; (iv) matrix swelling and dissolution arenegligible; (v) drug diffusivity is constant; and (vi) perfect sink conditions are always attained in the release environment.

In a general way it is possible to simplify the Higuchi model as :

$$f\,t = Q = K_H\,t^{1/2}$$

where,

KH is the Higuchi dissolution constant

The data obtained were plotted as cumulative percentage drug release versus square root of time.

4) Korsmeyer- Peppas model:

Korsmeyer et al. (1983) derived a simple relationship which described drug release from a polymeric system equation .

$$Mt / M\infty = K\,t^{n}.$$

where

Mt / M∞ is a fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as log cumulative percentage drug release *versus* log time.

S no	Release exponent (n)	Drug transport mechanism
1	0.5	Fickian diffusion
2	0.45 < n = 0.89	Non -Fickian transport
3	0.89	Case II transport Zero order release
4	Higher than 0.89	Super case II transport

6.2.7 Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a re-testing for the drug substance or a shelf-life for the drug product and recommended storage conditions.

The storage conditions used for stability studies were accelerated condition ($40^oC\pm 2^oC/75\% \pm 5\%$ RH) and room temperature ($30^oC\pm 2^oC/65\% \pm 5\%$ RH). Stability study was carried out for the optimized formulation. Tablets of optimized formulation were striped packed and kept in stability chamber for 3 months on above mention temperature.

Tests performed

1. Dissolution profile
2. Drug content uniformity
3. Test for other physical parameters

7. RESULTS AND DISCUSSION

In the present study bi layered tablets were prepared by combining Metformin hydrochloride floating sustained release layer and Sitagliptin immediate release layer.

7.1 PREFORMULATION STUDIES

7.1.1 METFORMIN HYDROCHLORIDE

A) Identification and characterization of the drug

i) Description

The sample was found to odorless, white, crystalline, hygroscopic bitter powder.

ii) Melting point

Melting point of the pure Metformin was found to be 223°-226° C which was within the limit as per the IP 1996.

iii) Solubility

Freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride.

IV) IR absorption spectrum

FT-IR spectrum of pure drug sample which was recorded using potassium bromide (KBr) pellets method was as follows:

Fig – 7.1: FT-IR spectrum of Metformin Hydrochloride

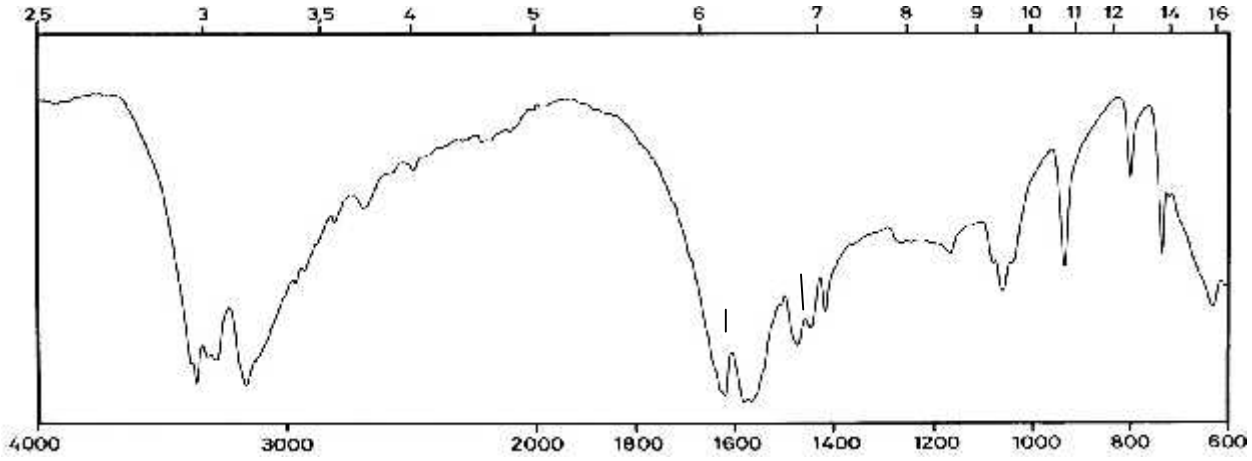


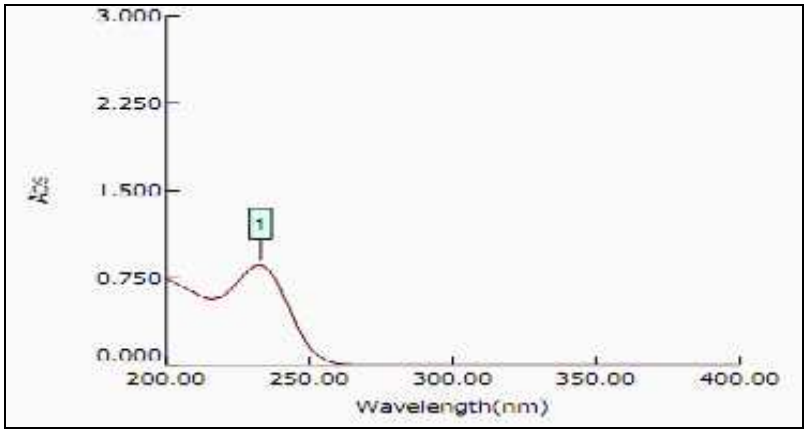
Table – 7.1 Data showing Observed and Reported peaks of Metformin Hcl.

Functional group	Vibrational Frequencies cm^{-1}	
	Observed peaks	Reported peaks
N-H deformation	1624.12 cm-1	1630 cm-1
Asymmetric NCN stretch	1570.11 cm-1	1565 cm-1
CH3 Asymmetric deformation	1473.66 cm-1, 1444.73 cm-1, 1415.66 cm-1	1470, 1440, 1410 cm-1
C-N stretch	1062.81 cm-1	1060cm-1
CH3 rock	937.44 cm-1	940 cm-1

V) UV spectra

UV- Spectra of pure Metformin Hcl was obtained from UV- Spectrophotometer and the absorption maximum was found to be 233 nm.

Fig – 7.2 UV spectrum of Metformin Hcl



The spectrum shows that the absorption maximum of Metformin Hcl is at 233 nm with absorbance of 0.854.

VI) Assay

The obtained sample of Metformin Hcl was found to be 99.76% w/w pure by assay method.

From the above results of drug characterization study it was observed that the sample of Metformin Hcl is pure and complies the Indian Pharmacopeial standards.

B) Calibration Curve For Metformin Hcl

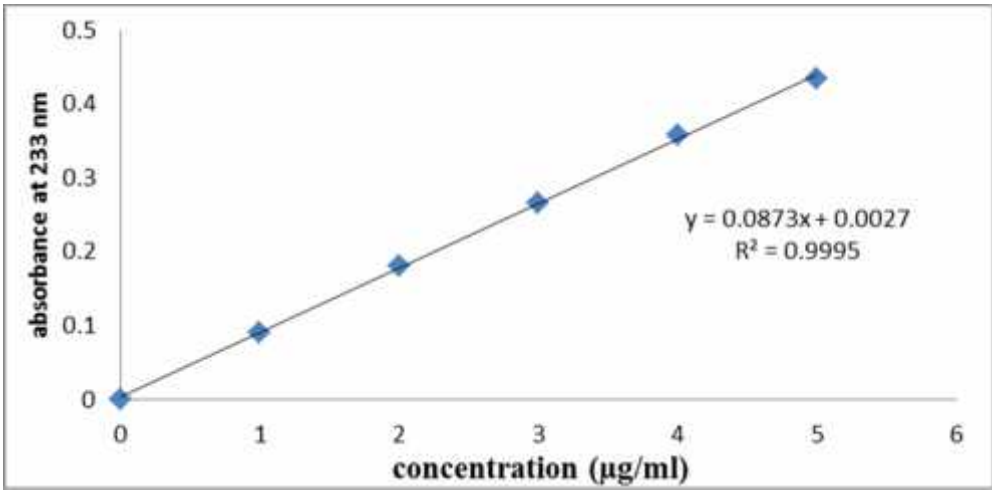
The calibration curve of the Metformin Hcl was plotted in by measuring Absorbance of different concentrations of samples (0-30 µg/ml) was measured at 233 nm. The regression coefficient was found to be 0.999 with slope value 0.087 .The results indicate that there is a linear relationship between concentration and absorbance and obey beer's Lambert's law.

$$y = 0.087x + 0.002$$

Table – 7.2 Data for calibration curve showing absorbance at 233 nm

S no	Concentration (µg/ml)	Absorbance at 233nm
1	0	0.00
2	1	0.09
3	2	0.18
4	3	0.265
5	4	0.357
6	5	0.434
	Slope	0.087
	Regression coefficient	0.999

Fig No – 7.3 Calibration curve of Metformin Hcl



C) Drug – Excipient Compatibility

FTIR Spectra of Pure Metformin HCl, HPMC K100M, sodium CMC, PVP K-30, lactose and the physical mixture of Metformin + HPMC K100M + sodium CMC + PVP K-30 were shown in Fig no: 7.4 to 7.7 .

Fig No -7.4 FT-IR spectrum of HPMC K100M

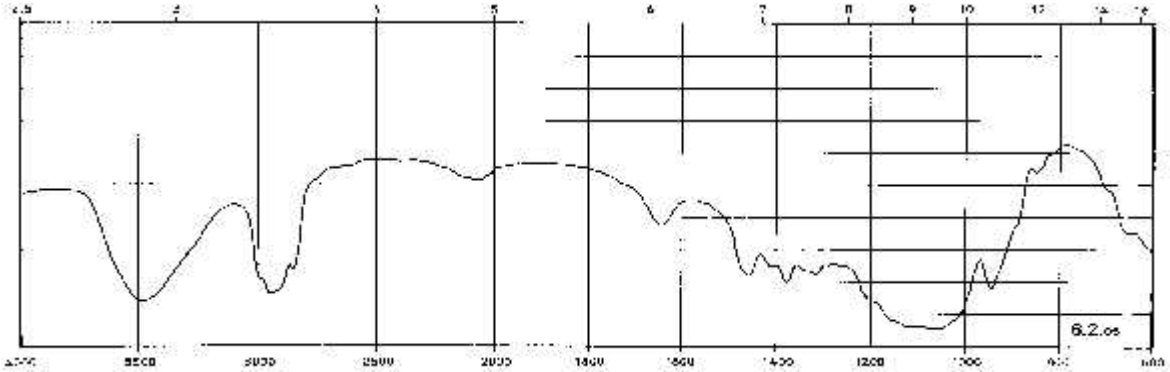


Fig No –7. 5 FT-IR spectrum of Sodium CMC

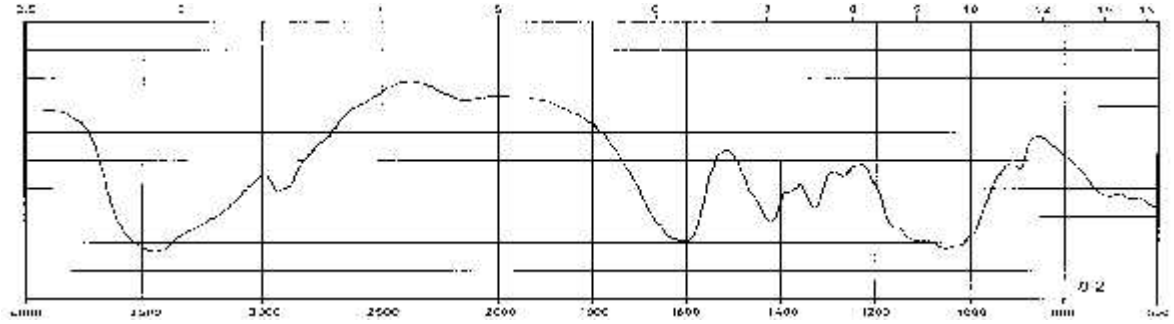


Fig no –7. 6 FT-IR spectrum of PVP K30

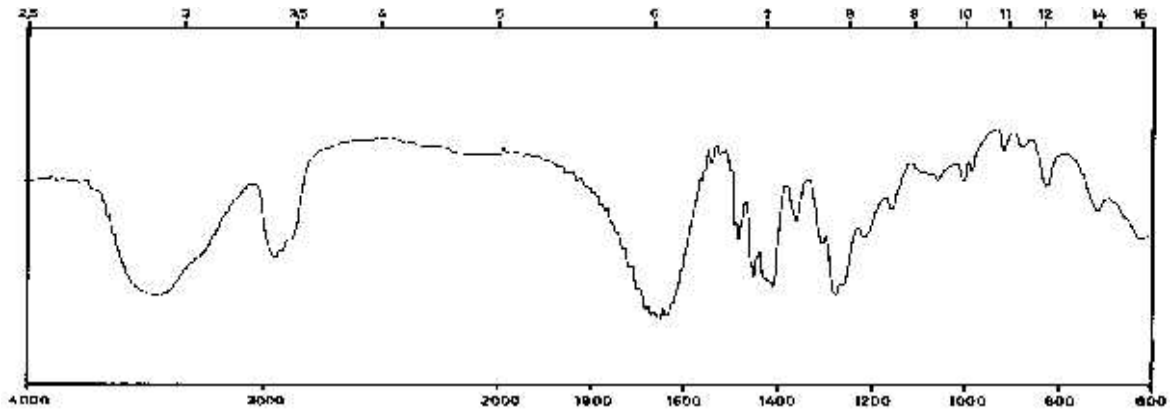
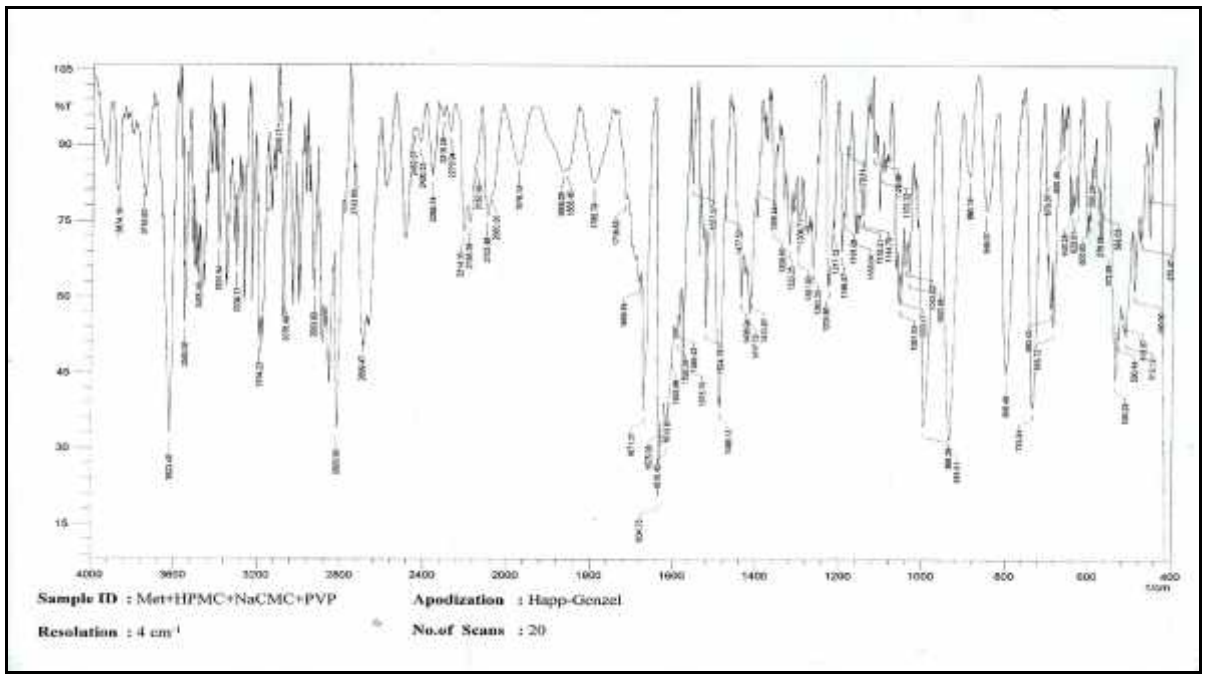


Fig No – 7.7 FT-IR spectrum of Metformin + HPMC K100M + sodium CMC+ PVPK30



From the Figure no 7.7 - It was confirmed that there is no interaction between drug and polymers because the IR spectra of all physical mixtures retains the principal drug peaks at :- 1624.12, 1570.11, 1062.81, 937.44 cm^{-1}

7.1.2 SITAGLIPTIN PHOSPHATE

A) Identification And Characterization

i) Description

Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder

ii) Melting point

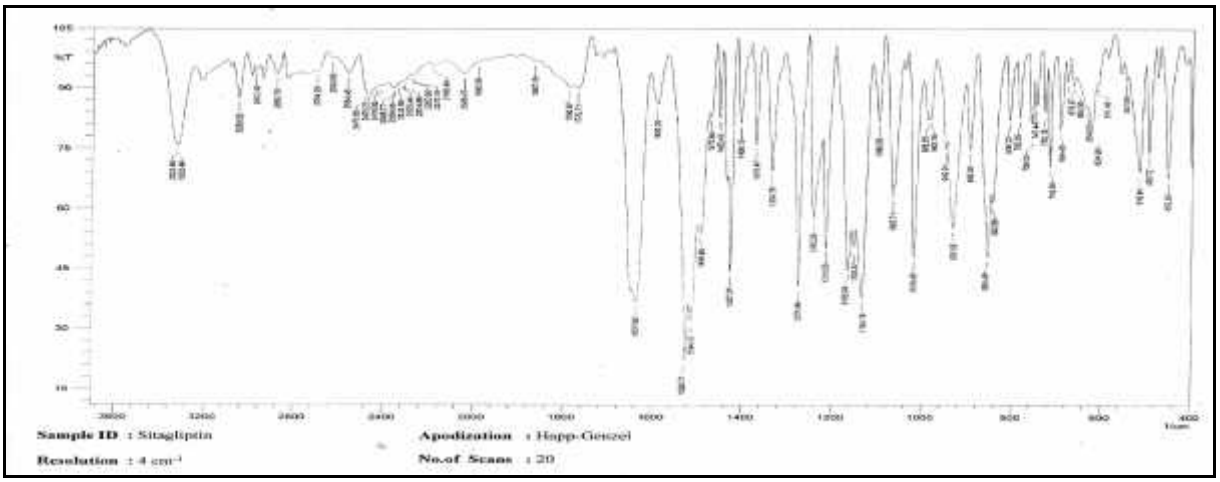
The melting point of Sitagliptin phosphate was found to be 198^{o}-202^{o} C which implies the purity of the drug**.**

iii) Solubility: It is slightly soluble in methanol, very slightly soluble in ethanol, acetone, and acetonitrile, and insoluble in isopropanol and isopropyl acetate. It is a BCS class 1 drug with high aqueous solubility and high permeability.

iv) IR absorption spectrum

FT-IR spectrum of Sitagliptin Phosphate drug sample was recorded using potassium bromide (KBr) pellet method and is as follows:

Fig no – 7.8 FTIR Spectrum of Sitagliptin Phosphate

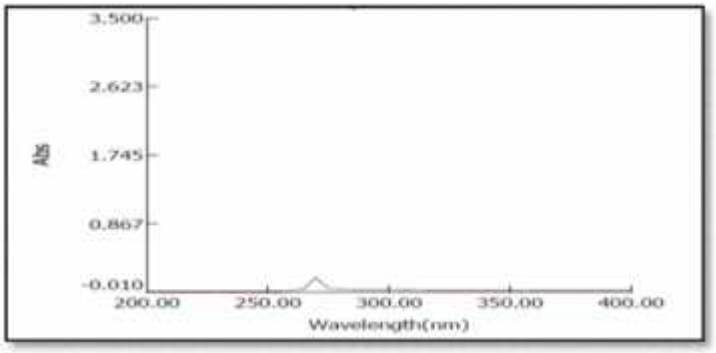


Principle drug peaks were found at 1018.45, 1066.62, 1637.62, 3050.52, 3323.46 cm^{-1}

V) UV spectra

UV- Spectra of pure Sitagliptin Phosphate was taken in 0.1N Hcl as the medium. Sample of 10µg/ml was scanned over wave length range of 400-200 nm.

Fig no –7.9 UV Spectum of Sitagliptin Phosphate.



Thus from the spectrum the absorption maximum was found to be 267 nm.

VI) Assay

The obtained sample of Sitagliptin Phosphate was found to be 99.76% w/w pure.

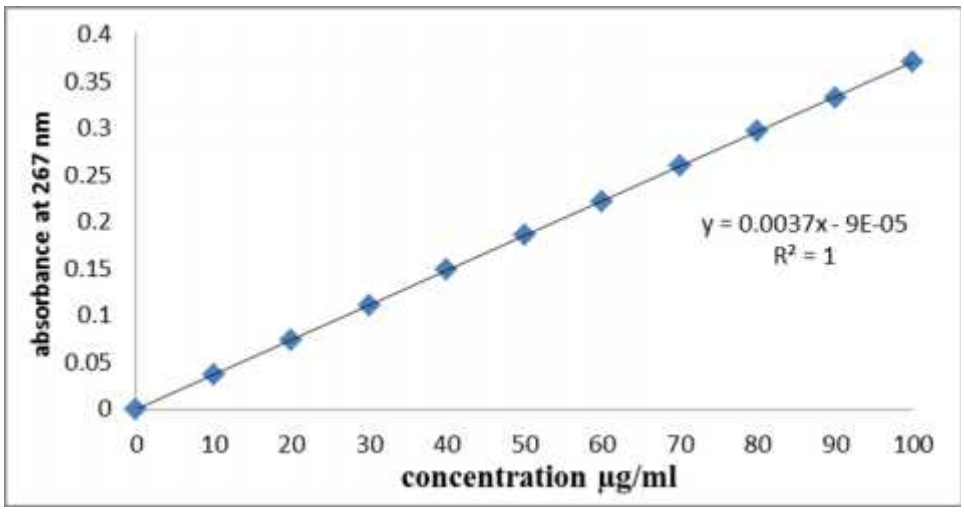
From the above results of drug chracterization study it was observed that the sample of Sitagliptin Phosphate was pure and complies the Indian pharmacopial standards.

B) Calibration Curve For Sitagliptin Phosphate

Table No –7. 3 Calibration curve of Sitagliptin phosphate at 267 nm.

Concentration (µg/ml)	Absorbance (nm)
0	0.00
10	0.037
20	0.073
30	0.111
40	0.149
50	0.186
60	0.221
70	0.26
80	0.296
90	0.332
100	0.371
Regression coefficient	1.00

Fig no – 7.10 Calibration curve of Sitagliptin Phosphate



C) Drug – Excipient Compatibility

Fig no –7.11 FTIR Spectrum Of pure Sitagliptin Phosphate

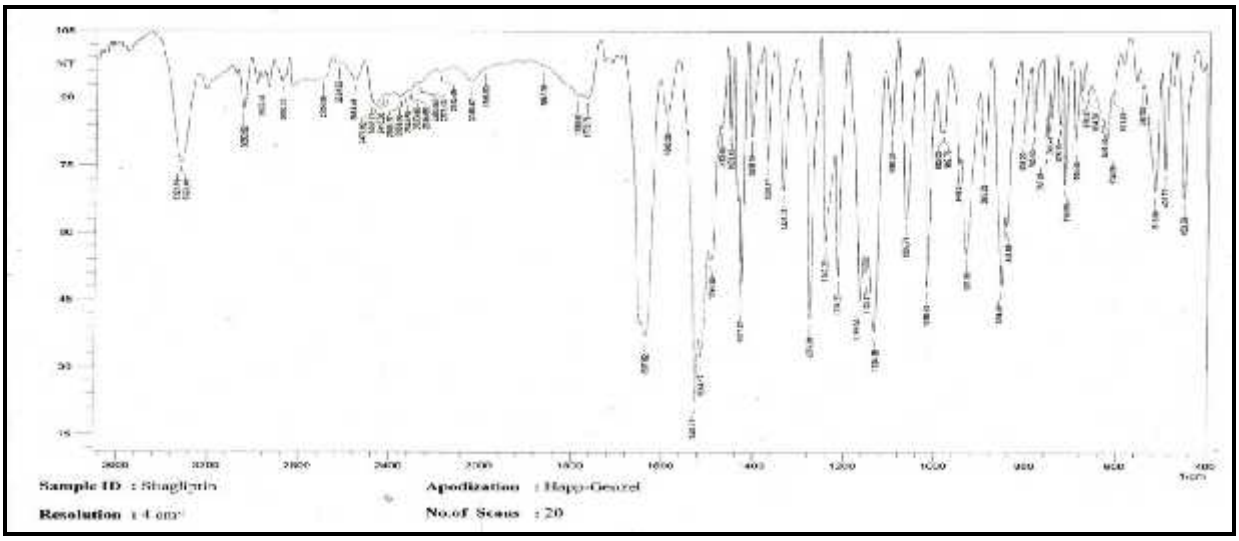


Table no – 7.4 Data of Infra Red peaks of Sitagliptin Phosphate.

Functional group	Vibrational Frequencies cm^{-1}	
	Observed peaks	**Reported peaks**
C-F str	1018.45 cm^{-1}	1016.34 cm^{-1}
C = O str	1637.62 cm^{-1}	1635.50 cm^{-1}
N tertiary amine str	1066.71 cm^{-1}	1068.45 cm^{-1}
AR – CH str	3050.52 cm^{-1}	3047.42 cm^{-1}
C =NH str	3323.46 cm^{-1}	3320.65 cm^{-1}

Fig no - 7.12 FTIR Spectrum of Sodium Starch Glycollate

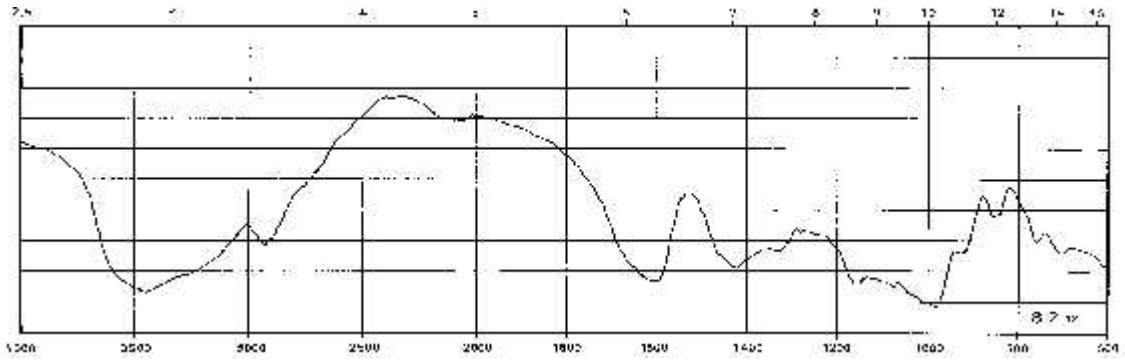


Fig no – 7.13 FTIR spectrum of crosspovidone

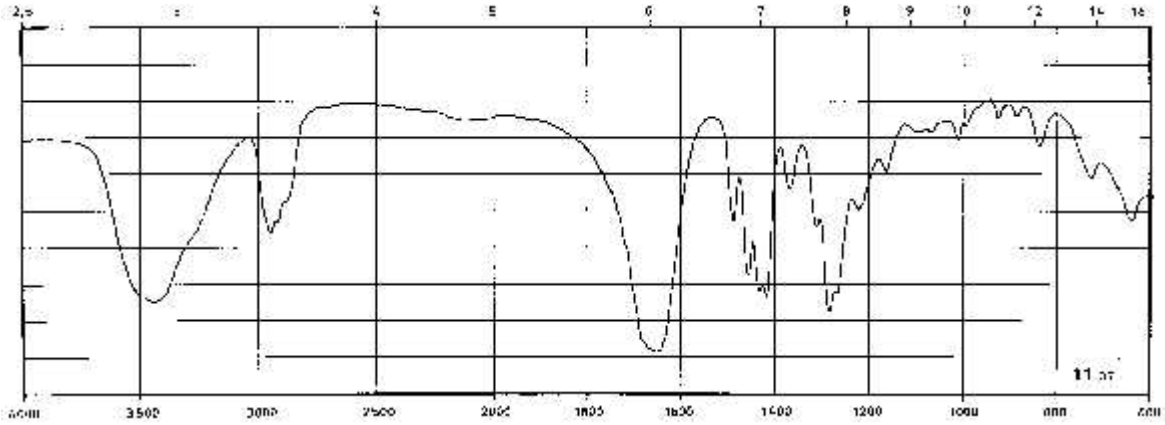


Fig no –7.14 FTIR Spectrum of PVP K30

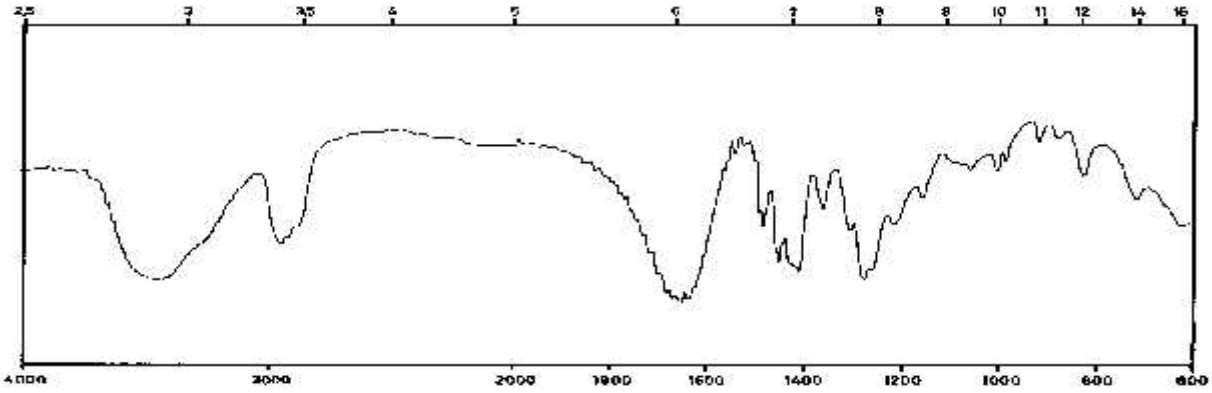
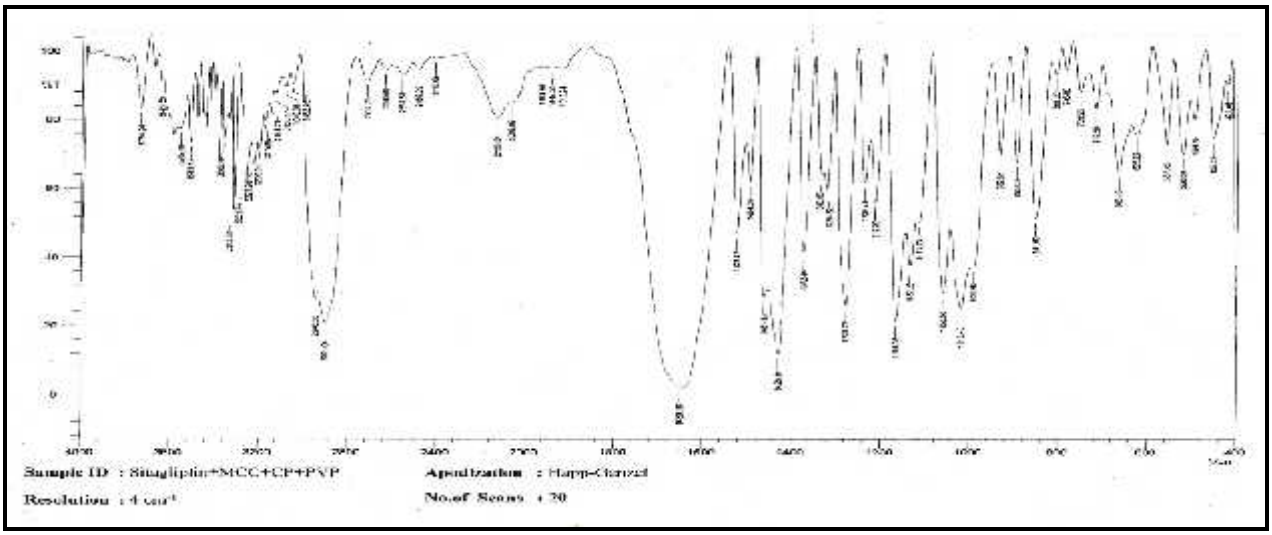


Fig no – 7.15 FTIR Spectrum of Sitagliptin + SSG + Crosspovidone + CCS + PVP K30



7.2 EVALUATION OF PRE COMPRESSION PARAMETERS

A) Evaluation of Metformin Hydrochloride Granules

Table No – 7. 4 Pre Compression Parameters of Metformin Hcl Granules

Formulation code	Angle of Repose (θ) (± SD)	Bulk Density (g/cc) (± SD)	Tapped Density (g/cc) (± SD)	Carr's Index (%) (± SD)	Hausner ratio (± SD)
F1	20.80±0.11	0.754±0.07	0.878±0.05	15.09±0.06	1.1644±0.05
F2	20.06±0.08	0.781±0.09	0.899±0.09	15.10±0.05	1.1510±0.07
F3	22.33±0.16	0.843±0.09	0.9302±0.11	15.68±0.09	1.1055±0.05
F4	22.97±0.12	0.735±0.12	0.836±0.08	14.52±0.06	1.1374±0.09
F5	20.68±0.09	0.764±0.14	0.891±0.09	16.62±0.13	1.1662±0.06
F6	22.16±0.11	0.782±0.08	0.902±0.08	15.34±0.08	1.1542±0.09
F7	21.83±0.12	0.767±0.09	0.883±0.13	15.12±0.11	1.1512±0.07
F8	21.62±0.09	0.781±0.12	0.895±0.09	14.59±0.05	1.1459±0.05
F9	20.85±0.13	0.792±0.15	0.910±0.11	14.89±0.05	1.1489±0.07
F 10	21.75±0.13	0.751±0.17	0.845±0.16	14.58±0.05	1.1251±0.07

(n=3, ± S.D) (S.D= Standard deviation)

The dried granules were evaluated for various granule properties as shown in table

- **Angle of repose**

  Angle of repose for the granules of F1-F9 was found to be 20.06 - 22.97^0, which indicates *good* flow property

- **Carr's index**

  The carr's index for the granules of F1-F9 was found to be 14.52 -16.62 %, which shows *good* flowing properties.

- **Hausner's Ratio**

  Hausner ratio was found to be 1.1055 – 1.1662 it indicates *good flow* properties of the granules.

B) Evaluation of Sitagliptin Blend

The directly compressible blend of different formulations of Sitagliptin was evaluated for angle of repose, Bulk and Tapped density, Compressibility index, Hausner's ratio. It showed that the results of all formulations of the granules were within limits and thus it confirmed that the granules have good flow property.

Table No – 7.5 Data for Pre Compression Parameters of Sitagliptin Blend

Formulation code	Angle of repose (θ) Mean ±S.D	Bulk density (gm/cc) Mean±S.D	Tapped density (gm/cc) Mean ±S.D	Compressibility index Mean ±S.D	Hausner's ratio Mean ±S.D
F1	25.58±0.31	0.74±0.01	0.99±0.02	17.64±1.2	1.40±0.02
F2	25.08±0.45	0.78±0.08	0.98±0.01	16.21±1.62	1.32±0.02
F3	24.47±0.21	0.78±0.06	0.96±0.08	16.66±0.79	1.15±0.01
F4	23.72±0.23	0.85±0.047	0.98±0.04	13.31±0.78	1.15±0.01
F5	23.40±0.15	0.86±0.047	0.99±0.04	12.50±0.44	1.14±0.05
F6	23.29±0.17	0.86±0.022	0.97±0.04	11.38±1.20	1.13±0.01
F7	22.68±0.09	0.88±0.047	0.98±0.01	13.84±0.90	1.12±0.01
F8	22.77±0.15	0.87±0.098	0.99±0.04	11.49±0.53	1.13±0.06
F9	22.49±0.08	0.88±0.021	0.98±0.01	12.54±0.42	1.12±0.05

(n=3, ± S.D) (S.D= Standard deviation)

- **Angle Of Repose**

  The angle of repose of all the 9 formulations was in the range of 22.49±0.08 to 25.58±0.31 which shows the *good* flow property of the sitagliptin immediate release blend.

- **Bulk And Tapped Density**

  The bulk and tapped density values were in the range of 0.74 - 0.88(gm/cc), and 0.97 - 0.99 (gm/cc), respectively.

- **Compressibility index**:

  The carr's index (or) Compressibility index for the blend of F1-F9 was found to be in the range of 11.38-17.64 showing *excellent to good* flow properties.

- **Hausner's Ratio**

  Hausner ratio was found to be in the range of 1.12- 1.40. It indicates good flow properties of the blend.

7.3 EVALUATION OF METFORMIN HCL FLOATING SR TABLETS

7.3.1 Floating Behavior / In Vitro Buoyancy Test

Compositions of the buoyant layer for floating testing were shown in Table 6.3 .When the tablet was immersed in a 0.1 N Hcl solution at 37 ^{0}C, it sank at once in the solution and the carbon dioxide gas started to generate from the floating layer containing sodium bi-carbonate due to a chemical reaction. Each formulation started to float at different floating lag times. The floating tablets slowly swelled due to the presence of hydrophilic water swellable polymers like HPMC K100M and sodium CMC.

All the formulations (F1 – F8) having 10 mg sodium bi carbonate floated around 4.8 to 7.0 min depending upon their apparent viscosity. The formulations F9 and F10 containing 25 mg and 50mg have shown the floating lag times of 3.0, 2.5 min respectively. This shows that increase in sodium bi carbonate concentration decreases floating lag time. The total floating times of all the formulations were above 24 hrs. The formulations F9 & F10 shown less total floating time due to the increase in the concentration of the effervescent agent.

7.3.2 Tablet Density

The density values of all the formulations were measured and were found to be in the range of 0.845 g/cc to 0.933 g/cc. Since the density of all the tablets was less than that of gastric fluids they have shown good floating property.

Table No – 7.6 Results For In Vitro Buoyancy Test and Tablet Density of the Metformin Hcl Tablets.

S No	Formulations code	Tablet density (g/cc)	Floating lag time (min) average (n-3)	Total Floating Time (Hr)
1	F1	0.856	5.4	>24
2	F2	0.924	5.9	>24
3	F3	0.845	7.0	>24
4	F4	0.916	5.0	>24
5	F5	0.924	5.2	>24
6	F6	0.933	4.8	>24
7	F7	0.856	4.9	>24
8	F8	0.867	5.2	>24
9	F9	0.886	3.0	12-24
10	F10	0.882	2.5	12-24

7.3.3 Swelling study

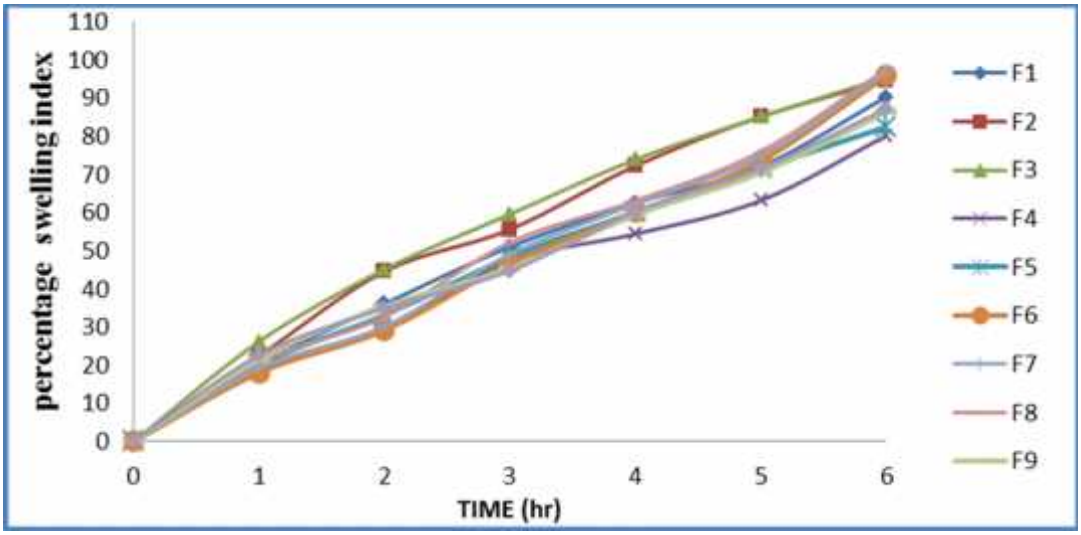
Table No – 7.7 Percentage Swelling Index of Metformin Hcl Tablets.

S no	Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	1	20.27	22.43	26.21	18.48	20.11	18.06	19.24	20.64	21.56	22.64
2	2	36.09	44.60	45.12	30.12	33.16	29.18	30.19	32.72	35.46	34.87
3	3	51.02	55.57	59.56	47.23	48.32	46.70	49.12	52.16	45.42	44.73
4	4	62.47	72.22	73.89	54.42	60.06	60.04	62.21	63.09	59.42	60.24
5	5	72.09	85.11	85.06	63.15	71.51	73.56	74.79	75.99	70.43	71.56
6	6	90.26	94.56	95.45	80.12	82.45	95.76	96.61	97.52	86.34	87.23

In the present study, F1 – F3 has HPMC K100 M shows more swelling than F4 & F5 having Sodium CMC because of high viscosity of HPMC. Then from F6-F9 the combination of two polymers increases swelling due to the synergistic increase in viscosity. Higher swelling index was found for tablets of batch F8 containing HPMC K100 M (100mg) and sodium CMC (75mg). Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability,

hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer

Fig no – 7.16 Plot Showing Swelling Index of Metformin SR Tablets



7.3.4 Post Compression Parameters Metformin Tablets

The Tablets from each Metformin formulation were evaluated for Average weight, Thickness, Hardness, Friability, weight variation and Uniformity in Drug content. The results were reported in Table no: 7.8

Shape and description of the tablets

Physical examination of the tablets shows that the tablets were capsule shaped with bisect on one side.

Tablet dimensions

The thickness of tablet was found to be in the range of 4.8 to 4.9 mm and was uniform from F1 – F10

Hardness: The hardness of the tablets was found to be in the range of 6.0 ± 0.2 to 6.5 ± 0.4 kg/cm^2 and was sufficient for the handling of tablets throughout the shelf life.

Friability

Percentage weight loss (or) % friability was measured and found to be in the range of 0.28 – 0.46 % and was within the pharmacopoeial limit that is less than 1% (F< 1%).

Weight variation test

The tablets of all the formulations (F1 – F10) passed the weight variation test as per USP limits as they have shown less than 5% of deviation from their weight.

Drug content uniformity

Drug content of Metformin Hcl found to in the range of 98.94 ±0.42 to 101.03 ±0.31%,was within the limit as per I.P and ICH guidelines.

Table No -7.8 Results For Post Compression Parameters Of Metformin Tablet.

Formulation	**Average Weight mg (n=20)**	**Hardness Kg/cm^2 (n=3)**	**Thickness mm(n=3)**	**Friability% (n=20)**	**Drug Content (%)**
F1	645.03 ±1.64	6.2 ± 0.3	4.8 ± 0.07	0.58	101.03±0.31
F2	670.14 ±1.91	6.5 ± 0.6	4.9 ± 0.05	0.48	99.86 ±0.70
F3	695.06 ±1.02	6.3 ± 0.2	4.8 ± 0.11	0.36	99.27 ±1.02
F4	645.52 ±2.83	6.5 ± 0.2	4.8 ± 0.08	0.56	99.61 ±0.73
F5	695.05 ±1.61	6.4 ± 0.4	4.8 ± 0.08	0.53	99.83 ±0.41
F6	670.12 ±3.90	6.5 ± 0.3	4.8 ± 0.13	0.54	100.83±1.13
F7	695.05 ±1.24	6.3 ± 0.2	4.9 ± 0.15	0.39	98.94 ±0.42
F8	720.09 ±1.61	6.4 ± 0.2	4.8 ± 0.09	0.48	101.02 ±1.1
F9	710.08 ±1.02	6.0 ± 0.4	4.9 ± 0.07	0.51	99.57 ±0.7
F10	735.50 ±1.02	6.5 ± 0.4	4.9 ± 0.07	0.40	99.21 ±0.7

(± S.D) (S.D= Standard deviation)

7.3.4 In Vitro Drug Release Study of Metformin Hcl Floating SR Layer Tablets

Table no – 7.9 Drug Release Profile of (F1- F5)

Time in hours	Cumulative percentage drug release				
	F1	**F2**	**F3**	**F4**	**F5**
0	0	0	0	**0**	**0**
1	35.23	30.11	28.46	33.38	30.23
2	52.62	47.15	43.65	50.29	48.66
4	69.24	59.61	57.62	67.24	62.46
6	82.36	72.48	70.54	79.56	74.41
8	91.74	81.69	79.52	88.32	83.62
10	97.03	89.54	87.35	98.63	89.65
12		94.85	91.25		94.57

Fig No – 7.17 Plot Showing The Drug release Profile of F1- F5

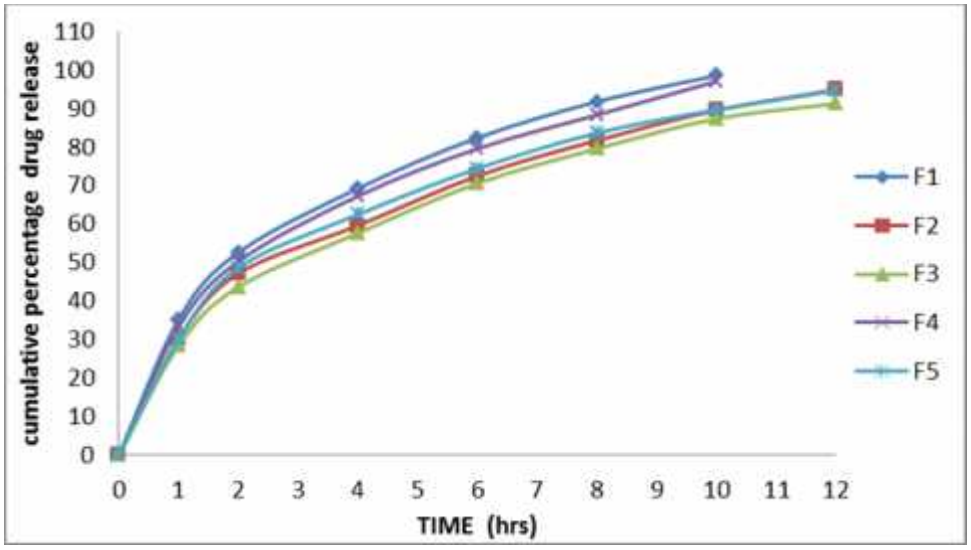


Table no- 7.10 Drug Release Profile of (F6- F8)

Time in hours	Cumulative percentage drug release		
	F6	**F7**	**F8**
0	0	0	0
1	29.23	22.06	20.56
2	45.05	34.5	31.23
4	61.43	51.21	48.47
6	78.2	71.02	68.25
8	87.23	82.31	78.85
10	96.46	92.84	89.34
12		98.73	95.52

Fig No – 7.18 Graph Showing The Dissolution Profile Of F6- F8

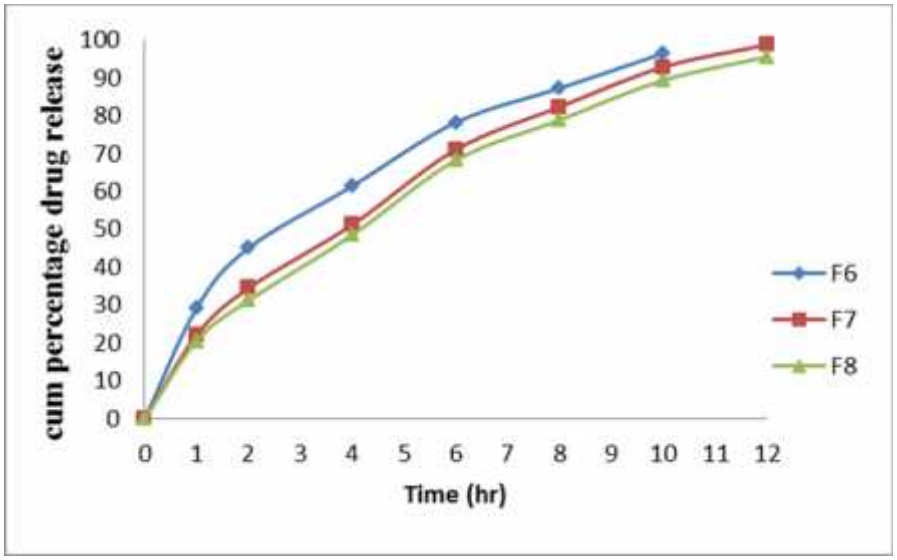


Table no – 7.11 Drug Release Profile of (F9- F10)

Time in hours	Cumulative percentage drug release	
	F9	**F10**
0	0	0
1	30.35	35.05
2	46.12	48.44
4	58.65	60.05
6	74.24	77.31
8	82.21	84.20
10	89.36	91.65
12	93.52	96.75

Fig No – 7.19 Graph Showing the Dissolution Profile of F9- F10

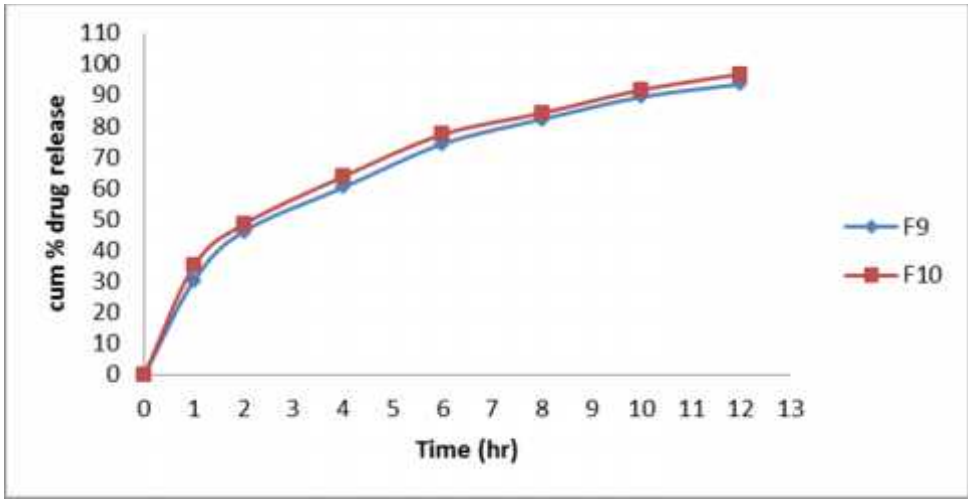
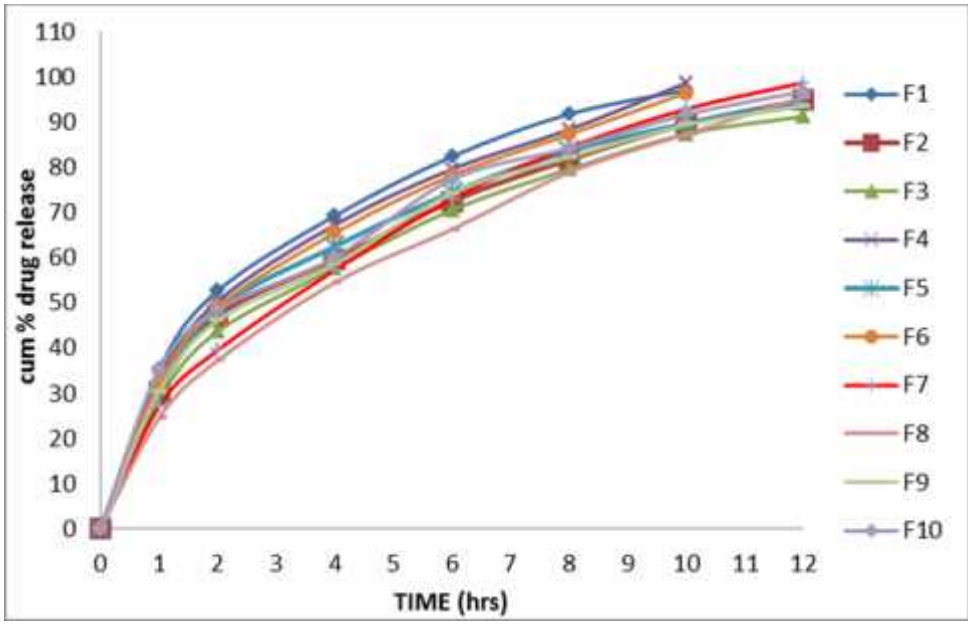


Table no – 7.1 Drug Release Profile of formulations F1 – F10

S no	Time	Cumulative percentage Drug Release									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	0	0	0	0	0	0	0	0	0	0	0
2	1	35.23	30.11	28.46	33.38	30.23	29.23	22.06	20.56	30.35	35.05
3	2	52.62	47.15	43.65	50.29	48.66	45.05	34.5	31.23	46.12	48.44
4	4	69.24	59.61	57.62	67.24	62.46	61.43	51.21	48.47	58.65	60.05
5	6	82.36	72.48	70.54	79.56	74.41	78.2	71.02	68.25	74.24	77.31
6	8	91.74	81.69	79.52	88.32	83.62	87.23	82.31	78.85	82.21	84.20
7	10	97.03	89.54	87.35	98.63	89.65	96.46	92.84	89.34	89.36	91.65
8	12		94.85	91.25		94.57		98.73	95.52	93.52	96.75

Fig no – 7.20: Comparative Drug Release Profile of F1 – F10



- In the formulations FI – F3 HPMC K100M was used as the release retarding polymer, being a hydrophilic swellable polymer it gradually swells with floating and sustains the release of the drug up to 12 hrs. From F1 to F3 the drug release rate decreases as the concentration of HPMC K100M increase from 100 mg to 150mg. In F1 as the concentration of HPMC K100M was 100 mg maximum (97.03%) drug released in 10 hrs. Among F1, F2, F3 as the concentration of HPMC K100M increases % drug release decreases.
- Further the trials were taken by taking sodium CMC as the rate retarding polymer. Formulations F4, F5 having 100mg and 150 mg of sodium CMC respectively shows less % drug release than same concentrations of HPMC K 100M . From F4 to F5 as the viscosity of sodium CMC increases the drug release decreases. In these formulations optimum drug release comparable to the marketed tablets was not obtained at the end of 12 hrs.
- Further in formulations F6 to F8 high viscosity polymer HPMC K100M was taken in combination with sodium CMC. Here HPMC concentration was kept constant and sodium CMC was increased in the range of 3.7 % - 10.4% w/w.
- Freely soluble drugs have been reported to be released slower from combinations of HPMC and Na CMC matrices than with HPMC alone, as the combination increases the viscosity due to a synergistic effect of the two polymers. Therefore in F6 – F8 as the concentration of sodium CMC increases from 3.7 % - 10.4% w/w the cumulative % drug release decreases. Here F7 shows better drug release by releasing 98.73% at the end of 12 hrs.
- Then further trials were taken to determine the effect of increasing concentrations of sodium bi-carbonate on floating lag time and % drug release. In formulations F9 to F10 as the concentration of sodium bicarbonate increases from 25 mg to 50 mg floating lag time decreased from 4.5-5.0 min to 3.0 and 2.5 min respectively.
- The drug release profile of F9 and F10 were compared with F3 having the same composition, results shows increase in % drug release by releasing 93.52 and 96.75 for F9 and F10 respectively when compared to F3 (91.25%).

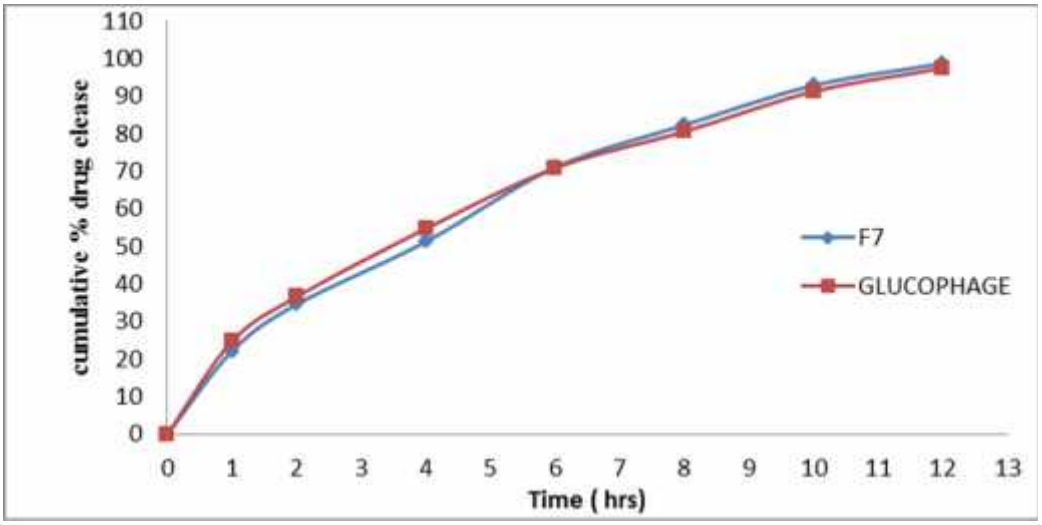
Hence, F7 was selected as the best formulation

7.3.5 Comparison of F7 with marketed formulation (GLUCOPHAGE XR).

Table no – 7.13 Comparision of F7 with Glucophage XR Tablets

S no	Time in hours	Cumulative % drug release	
		F7	Glucophage SR
1	0	0	0
2	1	22.06	24.65
3	2	34.5	36.54
4	4	51.21	54.68
5	6	71.02	70.85
6	8	82.31	80.56
7	10	92.84	91.24
8	12	98.73	97.45

Fig no – 7.20 Graph Showing Comparision Of F7 With GLUCOPHAGE XR Marketed Formulation.



7.4 EVALUATION OF SITAGLIPTIN IR TABLETS

7.4.1 Disintegration Test for Sitagliptin IR Tablets

Teble no – 7.14 Data Showing Disintegration Time For Sitagliptin IR tablets

S no	Formulation	Disintegration time (sec)
1	S1	98 ± 2.52
2	S2	75 ± 1.02
3	S3	58 ± 2.85
4	S4	92 ± 1.75
5	S5	69 ± 1.96
6	S6	56 ± 2.35
7	S7	84 ± 2.64
8	S8	59 ± 2.13
9	S9	54 ± 3.61

(n=3, ± S.D) (S.D= Standard deviation)

Disintegration time of the formulations S1 to S9 vary according to the varying concentrations of superdisintegrants like crosspovidone and croscarmellose sodium.

From S1 to S3 as Crospovidone concentration increases from (2-5%) disintegration time decreases gradually. Similarly from S4 – S6 as the concentration of Cros Carmellose Sodium increases from (2-5%) disintegration time decreases proportionally. Among the 2 superdisintegrants Croscarmellose Sodium gives less disintegration time of 56 sec.

Further more in formulations S7 - S9 Sodium Starch Glycolate was used as the superdisintegrants 2- 4%, as the concentration increases disintegration time decreases. Among the three superdisintegrants used SSG was the better disintegrant showing lesser DT time around 54 sec.

7.4.2 Post Compression Parameters of Sitagliptin IR Tablets

Formulation	Average Weight mg (n=20)	Hardness Kg/cm^2 (n=3)	Thickness mm(n=3)	Friability% (n=20)	Drug Content (%)
S1	250.03 ±1.64	3.4 ± 0.3	2.8 ± 0.07	0.58	99.03±0.31
S2	251.14 ±1.91	3.3± 0.6	2.9 ± 0.05	0.48	99.86 ±0.70
S3	250.06 ±1.02	3.3 ± 0.2	2.8 ± 0.11	0.36	99.27 ±1.02
S4	250.52 ±2.83	3.5 ± 0.2	2.7 ± 0.08	0.56	101.61 ±0.73
S5	251.05 ±1.61	3.6 ± 0.4	2.8 ± 0.08	0.53	98.83 ±0.41
S6	249.12 ±3.90	3.4 ± 0.3	2.7 ± 0.13	0.54	100.83±1.13
S7	252.05 ±1.24	3.2 ± 0.2	2.9 ± 0.15	0.39	98.94 ±0.42
S8	250.09 ±1.61	3.3 ± 0.2	2.8 ± 0.09	0.48	97.56 ±1.1
S9	250.08 ±1.02	3.5 ± 0.4	2.9 ± 0.07	0.51	99.63 ±0.62

(± S.D) (S.D= Standard deviation)

Weight Variation Test

The weights of the tablets were between 249.12 to 252.05 mg. the acceptable weight variation range is ±7.5%. Hence all tablets formulations passed the weight variation test.

Hardness

The hardness of all formulations was measured in kg/cm^2. Hardness of all formulations was in the ranged of 3.3 to 3.6 kg/ccm$^{2.}$

Friability: The friability values of none of the formulations exceeded 1% the results of friability indicate that the tablets were mechanically stable.

Thickness: Thickness of all the formulations was between 2.7 to 2.9 mm showings a fairly uniform tabletting.

Drug content: Drug content was uniform ranging from 97.56 ±1.1to 101.61 ±0.73.

7.4.3 In-Vitro Drug Release Profile of Sitagliptin IR Tablets

A) Drug Release profile of Sitagliptin IR Formulations SI – S3

Table no – 7.15 In Vitro Dissolution Profile of formulations (S1 – S3)

S no	Time (min)	Cumulative % drug release (% w/w)		
		S1	S2	S3
1	0	0	0	0
2	5	31.89	33.56	35.45
3	10	64.47	67.22	69.62
4	15	79.05	82.30	84.41
5	20	89.35	90.68	92.52
6	30	95.84	94.55	95.43
7	40	98.70	-	-
8	60	-	-	-

Fig No – 7.21 Graph Showing In Vitro Drug Release of (S1 – S3)

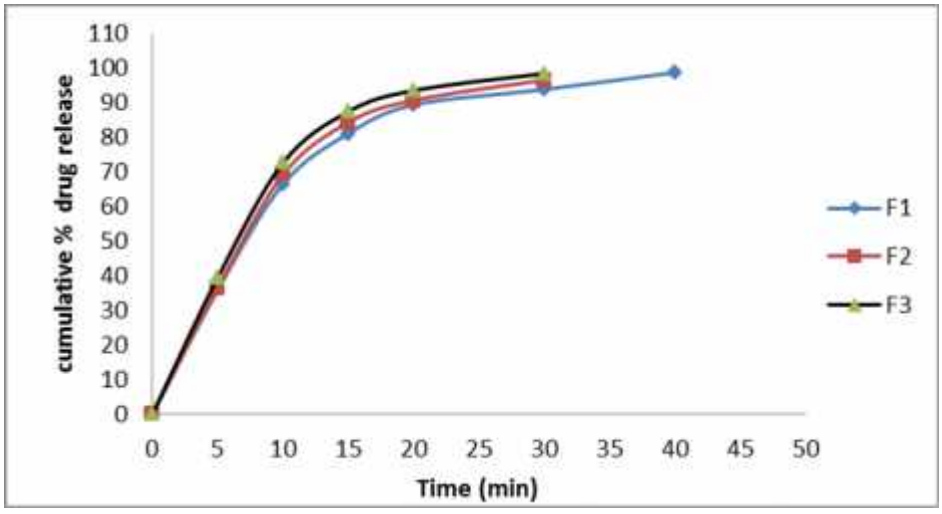
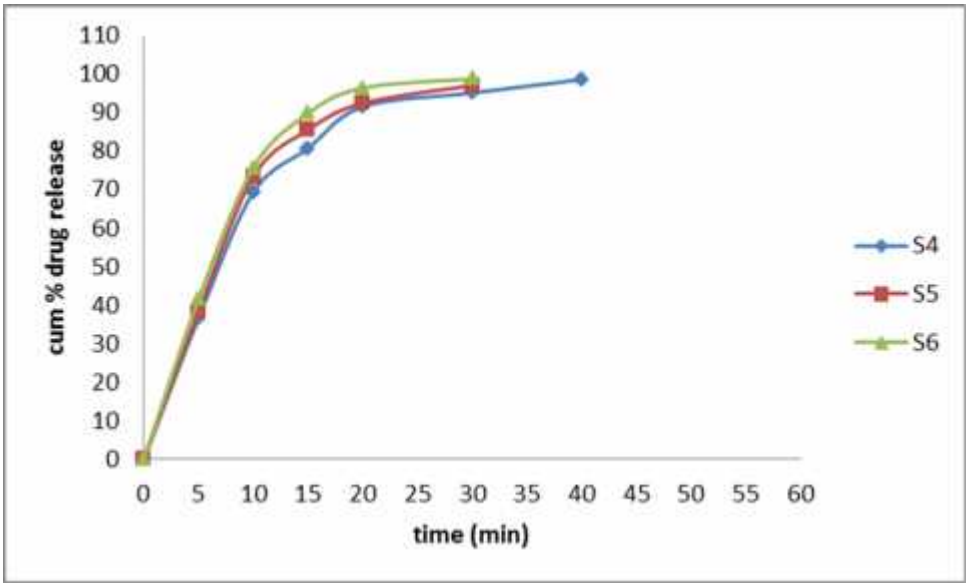


Table no - 7.16 In – Vitro Dissolution Profile For formulations (S4 – S6)

S no	Time (min)	Cumulative % drug release		
		S4	**S5**	**S6**
1	0	0	0	0
2	5	34.63	35.32	36.55
3	10	67.24	69.35	70.64
4	15	80.74	83.51	86.76
5	20	91.5	92.41	94.36
6	30	95.1	96.65	97.73
7	40	99.57	-	-
8	60	-	-	-

Fig No – 7.22 Graph Showing In Vitro Drug Release of (S4 – S6)



7.17 Table **no - In – Vitro Dissolution Profile For formulations (S7 – S9)**

S no	Time (min)	Cumulative % drug release		
		S7	**S8**	**S9**
1	0	0	0	0.00
2	5	35.47	37.22	38.55
3	10	68.61	70.36	72.64
4	15	85.73	88.65	89.64
5	20	90.12	95.37	97.86
6	30	94.24	97.64	99.64
7	40	-	-	-
8	60	-	-	-

Fig No – 7.23 Plot Showing In Vitro Drug Release of (S7 – S9)

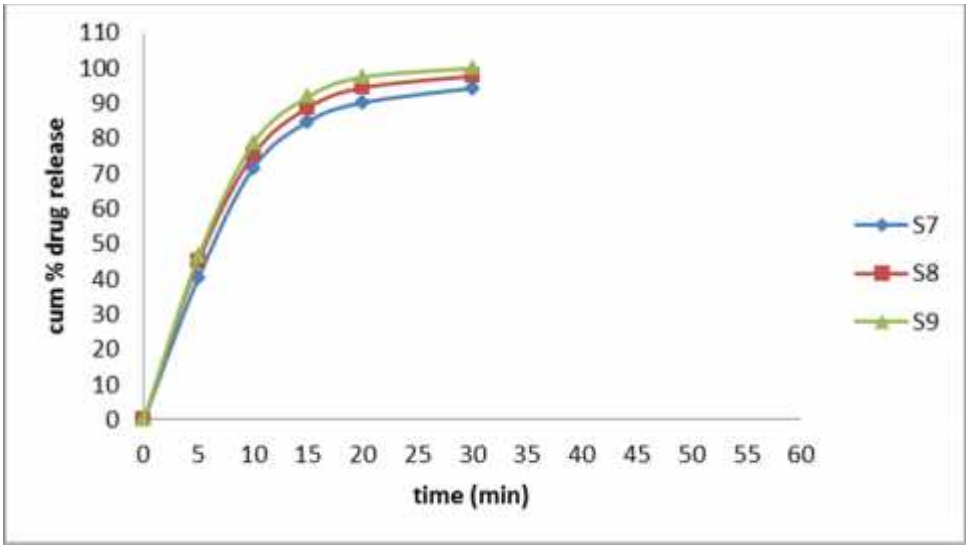
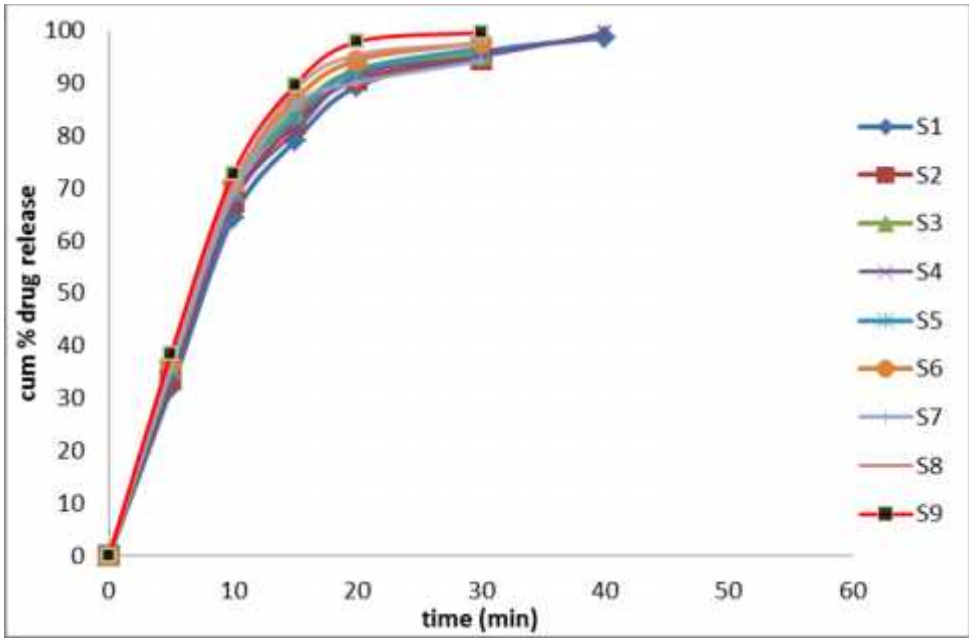


Table no – 7.18 Comparative Dissolution Profile for formulations (S1 – S9)

S no	Time	Cumulative percentage drug release								
	min	S1	S2	S3	S4	S5	S6	S7	S8	S9
1	0	0	0	0	0	0	0	0	0	0.00
2	5	31.89	33.56	35.45	34.63	35.32	36.55	35.47	37.22	38.55
3	10	64.47	67.22	69.62	67.24	69.35	70.64	68.61	70.36	72.64
4	15	79.05	82.30	84.41	80.74	83.51	86.76	85.73	88.65	89.64
5	20	89.35	90.68	92.52	91.5	92.41	94.36	90.12	95.37	97.86
6	30	95.84	94.55	95.43	95.1	96.65	97.73	94.24	97.64	99.64
7	40	98.70	-	-	99.57	-	-	-	-	-
8	60	-	-	-	-	-	-	-	-	-

Fig no – 7.24 Comparative drug release Profile For Sitagliptin IR formulations (S1- S9)



Discussion

In the formulations S1 – S3 cross povidone was used as super disintegrant in different proportions of 2%, 4%, 5% respectively. Therefore the drug release becomes faster from S1 to S3 with S3 showing 95.43 % after 30 min. From S4 – S6 cross carmellose sodium was used as super disintegrant in different proportions of 2-5% respectively. Therefore the drug release becomes faster from S4 to S6 with S6 showing 97.73% after 30 min.

Thus from formulations S1 to S6 it can be inferred that cross carmellose sodium was a better disintegrant giving faster release when compared to cross povidone. The % drug release of 5% of CCS in formulation S6 was not comparable to the marketed Sitagliptin IR tablets.

In formulations S7 – S9 sodium starch glycolate was used as the superdisintegrant 2-4% accordingly the % drug release increases with S9 giving 99.64 % at the end of 30 min. Among the three superdisintegrants used SSG has shown better drug release comparable to the marketed sitagliptin IR from JANUVIA 50mg.

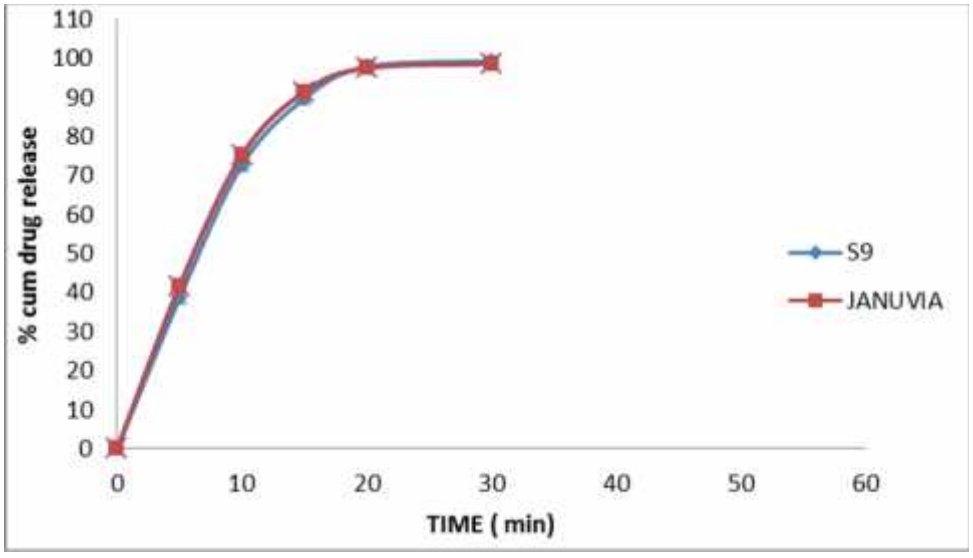
Hence S9 was selected as best formulation of Sitagliptin IR Layer.

7.45 Comparision Of best Sitagliptin IR formulation With Marketed tablets

Table no- 7.19 Comparision of S9 with Marketed (JANUVIA 50 mg)

S no	Time (min)	Cumulative % drug release	
		S9	JANUVIA 50 mg
1	0	0.00	0
2	5	38.55	41.65
3	10	72.64	75.17
4	15	89.64	91.42
5	20	97.86	97.52
6	30	99.64	98.64
7	40	-	-
8	60	-	-

Fig no – 7.2 Graph Showing Comparision of Drug Release Profile of S9 With Marketed Tablets



7.5 EVALUATION OF BILAYER TABLETS

7.5.1 Floating Behaviour of the bi layer tablets

S.no	Floating lag time (n=5) (± SD)	Total floating time (n=5) (± SD)	Tablet density (n=5) (± SD) (g/cc)
1	5.2 min	> 24 hrs	0.846

(± S.D) (S.D= Standard deviation)

7.5.2 Swelling Study

S no	Time (hr)	% Swelling Index
1	1	20.24
2	2	30.19
3	3	50.12
4	4	63.21
5	5	74.79
6	6	97.61

7.5.3 Disintegration test for Sitagliptin IR layer

S no	Disintegration time (sec) (n=6) (avg± SD)
1	52 ± 2.5

(± S.D) (S.D= Standard deviation)

7.5.4 Post compression parameters of the Bilayer tablets

Formulation	Average Weight mg (n=20) (± SD)	Hardness Kg/cm^2(n=3) (± SD)	Thickness mm(n=3) (± SD)	Friability %(n=20) (± SD)	Drug content (n=3)	
					Metformin Hcl	Sitagliptin
Bi Layer Tablet (F7 + S9)	945.07 ±1.38	6.7 ± 0.5	6.5 ± 0.63	0.75	99.67 ±0.42	99.63 ±0.7

(± S.D) (S.D= Standard deviation)

a) Shape and description of the tablets

Physical examination of the tablets shows that the bi - layered tablets were capsule shaped with bisect on one side, With clear differentiation of the two layers with colorless Metformin Hcl layer and sitagliptin layer having pale red colour.

b) Tablet dimensions

The thickness of tablets was found to be 6.5 ± 0.63 mm and was uniform in the batch.

c) Hardness

The hardness of the tablets was found to be 6.7 ± 0.5 kg/cm^2 and was sufficient for the handling throughout the shelf life.

d) Friability

Percentage weight loss (or) % Friability was measured and found to be in the range of 0.75 % and was within the pharmacopoeial limit that is less than 1% (F< 1%).

e) Weight Variation Test

The tablets of batch passed the weight variation test as per USP limits as they have shown less than 5% of deviation from their weight.

f) Drug Content Uniformity

Drug contents of Metformin Hcl and Sitagliptin in the bilayered tablet were found to 99.67 ±0.42 and 99.63 ±0.7 respectively. For both drugs their drug contents were within the limit as per I.P and ICH guidelines and have shown good content uniformity.

7.5.5 In Vitro Drug Release Profile of The Bi - Layer Tablet

Table no -7.20: In Vitro Drug Release Profile of the Bi - Layered Tablet (S9 – F7)

S. no	Time intervals	Cumulative % drug release	
		Sitagliptin IR S9	Metformin Hcl F7
1	0 min	0.00	0
2	5 min	37.85	0.53
3	10 min	72.05	2.36
4	15 min	88.64	5.42
5	20 min	97.20	8.37
6	30 min	99.15	13.56
7	40 min	100.10	19.34
8	60 min	-	21.56
9	2 h	-	33.75
10	4 h	-	52.40
11	6 h	-	71.02
12	8 h	-	81.31
13	10 h	-	92.20
14	12 h	-	97.65

Fig no – 7.25: In Vitro Drug Release Profile of the BiLayered Tablet (S9 – F7)

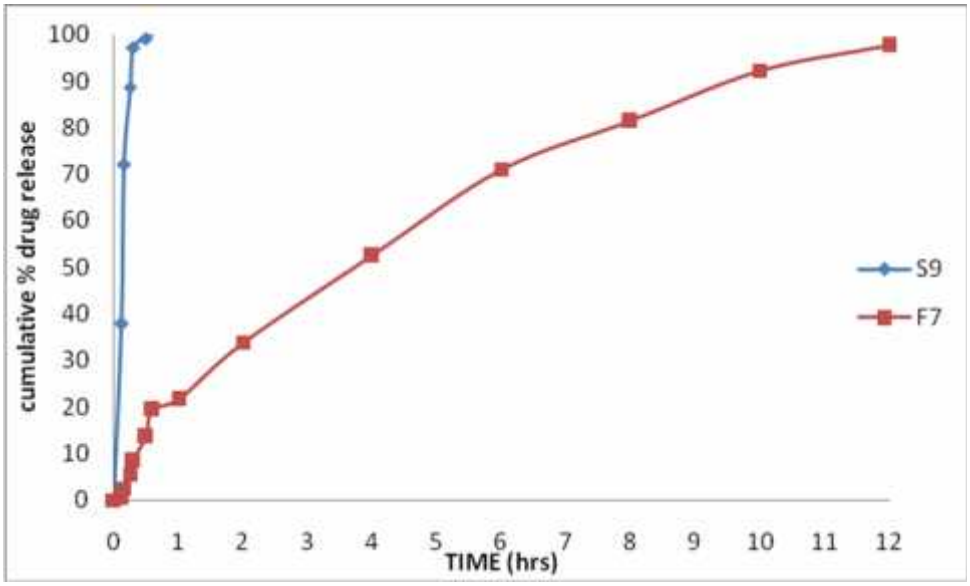


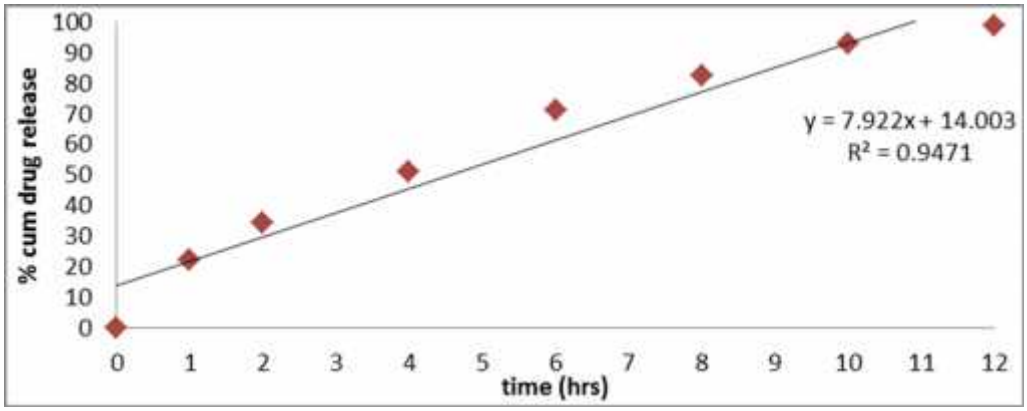
Table no -7.21 Comparision of drug release from bilayer tablet with marketed formulations

S no	Time intervals	Cumulative percentage drug release			
		S9	JANUVIA 50 mg	F7	GLUCOPHAGE XR 500 mg
1	0 min	0.00	0	0.00	-
2	5 min	37.85	41.65	0.53	-
3	10 min	72.05	75.17	2.36	-
4	15 min	88.64	91.42	5.42	-
5	20 min	97.20	97.52	8.37	-
6	30 min	99.15	98.64	13.56	-
7	40 min	100.10	-	19.34	-
8	60 min	100.32	-	21.56	24.65
9	2 h	100.33	-	33.75	36.54
10	4 h	100.46	-	52.40	54.68
11	6 h	100.39	-	71.02	70.85
12	8 h	101.32	-	81.31	80.56
13	10 h	101.35	-	92.20	91.24
14	12 h	101.38	-	97.65	97.45

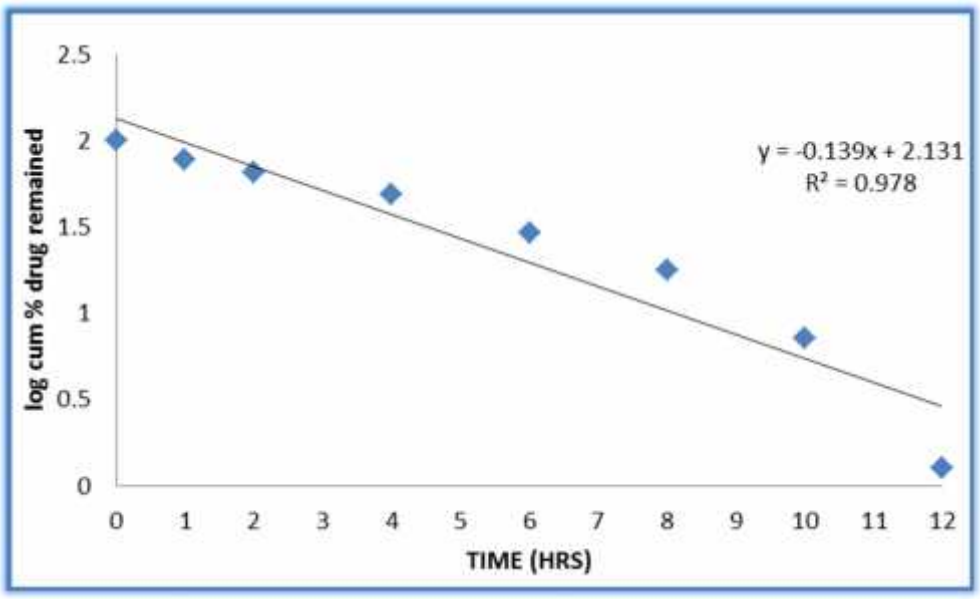
7.6 Kinetic study for Metformin SR layer of Bilayer Tablet

Evaluation of mechanism of drug release was done for the Metformin Hcl floating SR layer of the bi layer tablet (F7). In vitro drug release date was fitted into various kinetic models

A) Zero order : Graph of cumulative percentage of drug released and time

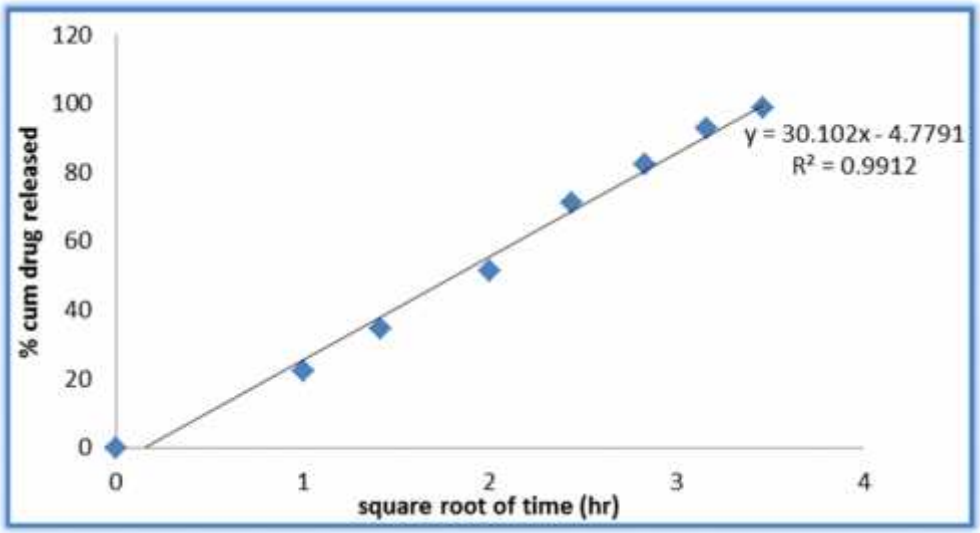


B) First order : Graph of log cumulative percentage of drug remaining and time.



C) Higuchi model :

Graph of cumulative percentage drug release and square root of time



D) Korsmeyer – peppas model :

Graph of log cumulative percentage drug release and log time.

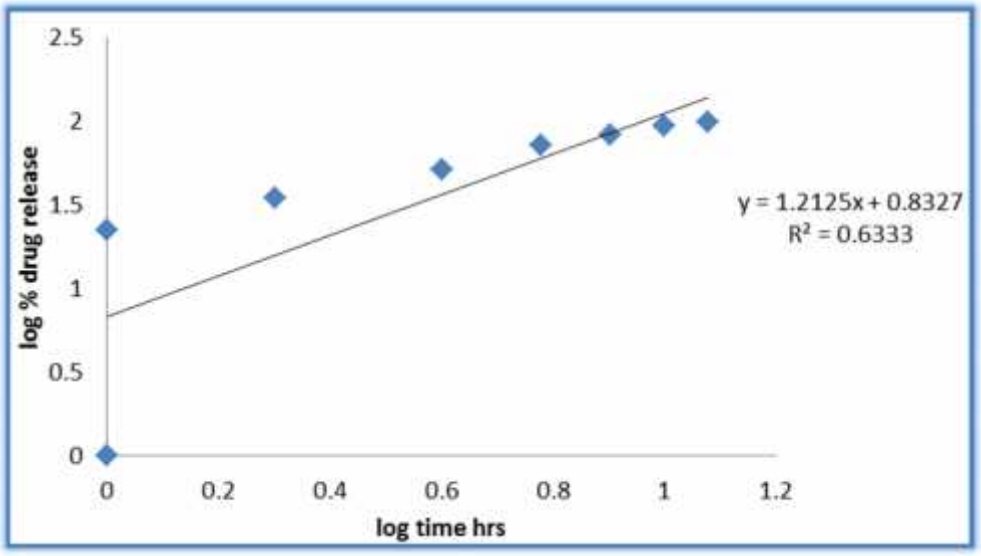


Table No – 7.22: Data for Kinetic Studies

S no	Time	$\sqrt{T}$	Log T	% CDR	log % CDR	Cum % drug remained	Log % cum drug remained
1	0	0	0	0	0	0	0
2	1	1.00	0	22.06	1.343	77.94	1.891
3	2	1.414	0.3010	34.5	1.537	65.50	1.816
4	4	2.00	0.602	51.21	1.709	48.90	1.689
5	6	2.44	0.7781	71.02	1.851	28.98	1.462
6	8	2.848	0.903	82.31	1.915	17.68	1.247
7	10	3.162	1.00	92.84	1.967	7.16	0.854
8	12	3.464	1.0791	98.73	1.994	1.27	0.103

Table no – 7.23 Results of kimetic studies for optimized formulation F7

S no	Formulation	Zero order R^2	First order R^2	Higuchi R^2	Koresmeyer peppas R^2	n	Mechanism of drug release
1	F7	0.947	0.978	0.991	0.633	0.617	First order non fickian diffusion

Mechanism of drug release

In order to understand the complex mechanism of drug release from the SR matrix system, the % in vitro release was fitted into Korsmeyer-peppas model and the release exponent value (n) was interpreted for mechanism of drug release. The release exponent value (n) thus obtained was 0.617 therefore, we can conclude that it follows **Non Fickian Diffusion mechanism.** The F 7 formulation exhibited **First order, Higuchi** mechanism**.**

7.7 Stability Studies

Stability studies

The selected formulation was evaluated for stability by conducting accelerated stability studies. The formulation were stored at 40^{o} C at 75% RH for 3 months and analyzed for their physical parameters and drug content and in vitro drug release studies at every one month interval. The data were shown in the table no 7.23.

Table No – 7.24:Characteristics of bi layered Tablet during stability studies

Time interval	Drug content (%w/w)		Hardness (Kg/cm^2)	Friability (%)
	Metformin Hcl	Sitagliptin		
After one month	99.68±0.42	99.63 ±0.62	6.60 ± 0.64	0.31
After two months	98.90 ± 0.12	99.35 ±0.45	6.50 ± 0.55	0.31
After three months	98.45 ± 0.08	98.94 ±0.67	6.5 ± 0.43	0.32

(± S.D n = 3) (S.D= Standard deviation)

Table No –7. 25: In vitro drug release profile of Metformin Hcl layer

Time in hours	Cumulative % drug release		
	1st Month	2nd Month	3rd Month
0	0.00	0.00	0.00
1	22.06	22.25	22.3
2	34.5	33.75	33.90
4	51.21	50.80	50.55
6	71.02	70.84	70.43
8	82.31	82.07	81.75
10	92.84	92.41	92.06
12	98.73	98.26	98.05

Table No –7. 26: In Vitro Drug release profile of Sitagliptin layer

Time in hours	Cumulative % Drug Release		
	1st Month	2nd Month	3rd Month
0	0	0	0
5	38.46	38.32	38.85
10	72.60	72.05	71.95
15	89.54	89.25	89.20
20	97.72	97.05	97.04
30	99.44	99.20	99.15
40			

THE PREPARED BILAYER TABLETS

9. CONCLUSION

In the present study an attempt was made to design a combination bi layer tablet containing Metformin Hcl gastro retentive floating sustained release layer and Sitagliptin immediate release layer.

FT - IR studies reveal that there were no significant interactions between both the drugs and between the drugs and their respective excipients.

For achieving sustained release of Metformin two hydrophilic swellable polymers like HPMC K100M and sodium CMC were used. Here, F7 containing combination of both polymers gave better sustained release for 12 hrs when compared to individual polymers. Formulation F7 gave 98.73 % W/V drug release after 12 hrs. Therefore F7 was selected as best formulation among F1-F10 and it is comparable to marketed Metformin tablets (GLUCOPGAGE XR).

For achieving immediate release of Sitagliptin, From the results it was concluded that disintegration activity decreases in the order of Cross Povidone < Cross Carmellose Sodium < Sodium Starch Glycolate i.e from S1 to S9 disintegration time decreases and % cumulative drug release increases. Thus S9 releasing 99.86 % after 30 min was selected as best formulation and is comparable to the marketed Sitagliptin tablets (JANUVIA).

Good floating behaviour was achieved by using sodium bicarbonate. In formulations F9-F10 as the concentration of sodium bicarbonate was increased the floating lag time decreased with minimal decrease in total floating time and % drug release increased when compared to F3 having same concentration of HPMC K100M.

The bilayer tablets prepared by taking F7 and S9 as two layers have shown good floating behaviour, good post compression parameters like hardness, friability weight variation drug content etc which were within the limits. Both the drugs in bilayer tablets shown dissolution profiles comparable with that of their respective marketed tablets.

Since, HPMC is a good hydrophilic polymer which ensures integrity of the gel layer causing slow diffusion of the drug through matrix. The combination of HPMC K100M and Sodium CMC gave good sustained drug release for 12 hrs when compared to HPMC alone due to increase in the viscosity by synergistic effect of the two polymers.

From this study by preparing bilayer tablets, it was concluded that we could reduce the total dose, dosage frequency, dose related side effects, and improve the bioavailability of Metformin which in turn improves the patient compliance.

Thus a fixed dose combination tablet of Metformin and Sitagliptin were designed as bilayer tablets which will have good patient compliance over their individual marketed counterparts.

However, further clinical studies are needed to access the utility of this system.

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